methyl-7-methoxyquinoline (17.7 mg, 100 µmol) in CH_2Cl_2 (3 mL). The solution was cooled to 0°C under a blanket of N_2 and then 250 µL of a 1.0 M solution of BBr_3 in hexanes (250 µmol, 2.5 equiv) was added at once by syringe. The stirred solution was warmed to rt and allowed to react for 3 h. The reaction was quenched with H_2O (1 mL), neutralized with sat. $NaHCO_3$ (4 mL) and extracted with CH_2Cl_2 (5 x 50 mL), dried over Na_2SO_4 and concentrated to give 12 mg (66%) of the desired phenolic quinoline as a light yellow oil. Data for (*R/S*)-1,2,3,4-tetrahydro-7-hydroxy-4-methylquinoline: $R_f = 0.15$ (hexanes/EtOAc, 3:1); ^{1}**H NMR** (400 MHz, $CDCl_3$) 6.91 (d, *J* = 8.7, 1 H), 6.12 (dd, *J* = 2.5, 8.3, 1 H), 5.97 (d, *J* = 2.5, 1 H), 3.27 (m, 2 H, C2-H), 2.84 (m, 1 H, C4-H), 1.95 (m, 1 H, C3-H), 1.66 (m, 1 H, C3-H), 1.25 (d, *J* = 6.9, 3 H, C4-CH_3).

(*R/S*)-1,2,3,4-Tetrahydro-4-methyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound **410**, structure **33A** of **Scheme XL**, where R^{1-3}=R^6=H, R^4=methyl, R^5=trifluoromethyl). In an oven dried pressure tube equivuipped with a magnetic stir bar was dissolved (*R/S*)-1,2,3,4-tetrahydro-7-hydroxy-4-methylquinoline (11.7 mg, 64.6 µmol) and trifluoromethyl ethyl acetoacetate (20 µL, 146 µmol, 2.2 equiv) and $ZnCl_2$ (20 mg) in 0.5 mL absolute ethanol. The light yellow solution was heated at 98 °C for 20 h and cooled to rt. The dark green solution was concentrated on Celite™ to give a free flowing powder which was purified *via* silica gel flash column chromatography using a solvent system of hexanes/ethyl acetate (4:1) to give 12.4 mg (66%) of Compound **410** as a yellow solid. Data for Compound **410**: $R_f = 0.19$ (hexanes/EtOAc, 3:1); ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.29 (s, 1 H), 6.36 (m, 2 H), 4.70 (br s, 1 H, NH), 3.43 (m, 2 H, C2-H), 2.95 (m, 1 H, C4-H), 1.97 (m, 1 H, C3-H), 1.72 (m, 1 H, C3-H), 1.31 (d, *J* = 7.0, 3 H, C4-CH_3).

EXAMPLE 311

1,2-Dihydro-2,2-dimethyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound **411**, structure **37A** of **Scheme XLI**, where R^{1-2}=R^6=H, R^3=R^4=methyl, R^5=trifluoromethyl, X=O)

1,2-Dihydro-2,2-dimethyl-7-(1,1,1-trimethylacetoxy)quinoline (structure **36A** of **Scheme XLI**, where R^1=R^2=H, R^3=R^4=methyl, P=*t*-butyl, X=O). In a oven dried pressure tube equivuipped with a magnetic stir bar was dissolved *O*-pivaloyl-3-aminophenol (EXAMPLE

138) (4.8 g, 25.0 mmol, 1.5 equiv) and 3-methyl-3-acetoxy-1-butyne (2.1 g, 16.7 mmol, 1 equiv) in dry THF (~5 mL). To the stirred solution was added CuCl (240 mg, 25 mmol, 0.15 equiv). The sealed pressure tube was heated at 98 °C for 5 h, cooled to rt and concentrated on Celite™ to give a free flowing powder which was purified *via* flash column chromatography (silica gel, hexanes/EtOAc, 5:1) to give 1.2 g (18%) of the desired product as an off white solid. Data for 1,2-dihydro-2,2-dimethyl-7-(1,1,1-trimethylacetoxy)quinoline: $R_f = 0.80$ (hexanes/EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) 6.83 (d, $J = 8.0$, 1 H), 6.23 (m, 2 H), 6.12 (d, $J = 2.1$, 1 H), 5.42 (d, $J = 9.7$, 1 H), 3.67 (br s, 1 H), 1.31 (s, 9 H), 1.29 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) 177, 151, 130, 127, 123, 117, 109, 105, 52, 49, 31, 27.

1,2-Dihydro-7-hydroxy-2,2-dimethylquinoline. To a oven dried rb flask was dissolved 1,2-dihydro-2,2-dimethyl-7-(1,1,1-trimethylacetoxy)quinoline (48 mg, 185 μmol) in absolute ethanol (5 mL) and H_2O (1 mL). To the stirred solution was added a catalytic amount of 20% aqueous NaOH solution (~0.2 mL). After 1.5 h the dark purple solution was diluted with H_2O (10 mL), EtOAc (15 mL) and quenched with sat. NH_4Cl solution (5 mL). The bi-phasic solution was extracted with EtOAc (4 x 20 mL), washed with brine (2 x 30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give 31 mg (96%) of the desired phenolic amine, which was used without further purification.

1,2-Dihydro-2,2-dimethyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound **411**, structure **37A** of **Scheme XLI**, where $R^{1-2}=R^6=H$, $R^3=R^4=$methyl, $R^5=$trifluoromethyl, X=O). In a oven dried pressure tube equivuipped with a magnetic stir bar was dissolved 1,2-dihydro-7-hydroxy-2,2-dimethylquinoline (31 mg, 177 μmol), ethyl (4,4,4-trifluoroacetoacetate) (75 mg, 408 μmol, 2.2 equiv) and $ZnCl_2$ (75 mg, 550 μmol, 3 equiv) in absolute EtOH. Upon addition of the $ZnCl_2$ the solution went a dark brown. The sealed pressure tube was heated at 105 °C for 16 h, cooled to rt and concentrated on Celite™ to give a free flowing powder which was purified *via* flash column chromatography (silica gel, hexanes/EtOAc, 5:1) to give 2.3 mg (4.4%) of Compound **411** as a bright yellow solid. Data for Compound **411**: $R_f = 0.31$ (hexanes/EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$)

7.11 (s, 1 H), 6.41 (s, 1 H), 6.32 (s, 2 H), 5.58 (d, *J* = 8.0, 1 H), 4.39 (br s, 1 H), 1.55 (s, 6 H).

EXAMPLE 312

1,2,3,4-Tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound 412, structure **40A** of **Scheme XLII**, where R^{1-2}=R^6=H, R^3=R^4=methyl, R^5=trifluoromethyl, X=O).

1,2,3,4-Tetrahydro-2,2-dimethyl-7-(1,1,1-trimethylacetoxy)quinoline (structure **39A** of **Scheme XLII**, where R^1=R^2=H, R^3=R^4=methyl, P=*t*-butyl, X=O). To a oven dried 250 mL rb flask equivuipped with a magnetic stir bar and a N_2 gas inlet was dissolved 1,2-dihydro-2,2-dimethyl-7-(1,1,1-trimethylacetoxy)quinoline (EXAMPLE 311) (47 mg, 192 µmol) in dry EtOAc (5 mL). The flask was repeatedly evacuated and flushed with N_2 then a catalytic amount of 10% Pd on C (~10 mg) was added. The flask was again evacuated and flushed with N_2 several times and then H_2 was introduced by balloon. The solution was stirred under H_2 for 13 h. The flask was again evacuated and flushed with N_2 several times to remove any residual H_2 and the solution was filtered through a pad of Celite™ and concentrated *in vacuo* to give the desired amine (38.0 mg, 154 µmol, 81% yield) as an off white solid. Data for 1,2,3,4-tetrahydro-2,2-dimethyl-7-(1,1,1-trimethylacetoxy)quinoline: R_f = 0.54 (hexanes/EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) 6.93 (d, *J* = 8.1, 1 H), 6.26 (dd, *J* = 2.3, 8.1, 1 H), 6.13 (d, *J* = 2.1, 1 H), 3.59 (br s, 1 H), 2.73 (t, *J* = 6.7, 2 H), 1.67 (t, *J* = 6.7, 2 H), 1.32 (s, 9 H), 1.18 (s, 6 H).

1,2,3,4-Tetrahydro-7-hydroxy-2,2-dimethylquinoline. To a oven dried rb flask was dissolved 1,2,3,4-tetrahydro-2,2-dimethyl-7-(1,1,1-trimethylacetoxy)quinoline (38 mg, 154 µmol) in absolute ethanol (5 mL) and H_2O (1 mL). To the stirred solution was added a catalytic amount of 20% aqueous NaOH solution (~0.2 mL) and stirred under N_2 at rt. After 3 h the dark purple solution was diluted with H_2O (10 mL), EtOAc (15 mL) and quenched with sat. NH_4Cl solution (5 mL). The bi-phasic solution was extracted with EtOAc (4 x 20 mL), washed with brine (2 x 30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give 25 mg (92%) of the desired phenolic amine as a light yellow oil. Data for 1,2,3,4-tetrahydro-7-hydroxy-2,2-dimethylquinoline: R_f = 0.22 (hexanes/EtOAc, 3:1); ^{1}H NMR (400 MHz,

$CDCl_3$) 6.82 (d, *J* = 8.1, 1 H), 6.09 (dd, *J* = 2.6, 8.2, 1 H), 5.93 (d, *J* = 2.4, 1 H), 2.68 (t, *J* = 6.7, 2 H), 1.67 (t, *J* = 6.7, 2 H), 1.19 (s, 6 H).

1,2,3,4-Tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyranono[5,6-g]quinoline (Compound **412**, structure **40A** of Scheme **XLII**, where R^{1-2}=R^6=R^8=H, R^3=R^4=methyl, R^5=trifluoromethyl, X=O,). In a oven dried pressure tube equivuipped with a magnetic stir bar was dissolved 1,2,3,4-tetrahydro-7-hydroxy-2,2-dimethylquinoline (25.1 mg, 142 µmol), TFEEA (62 mg, 338 µmol, 2.2 equiv) and $ZnCl_2$ (62 mg, 462 µmol, 3 equiv) in absolute EtOH. The sealed pressure tube was heated at 105 °C for 13 h, cooled to rt and concentrated on Celite™ to give a free flowing powder which was purified *via* flash column chromatography (silica gel, hexanes/EtOAc, 5:1) to 26.3 mg (60%) of Compound **412** as a bright yellow solid. Data for Compound **412**: R_f = 0.31 (hexanes/EtOAc, 3:1); ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.26 (s, 1 H), 6.37 (m, 2 H), 4.52 (br s, 1 H)m, 2.83 (t, *J* = 6.6, 2 H), 1.74 (t, *J* = 6.6, 2 H), 1.28 (s, 6 H).

EXAMPLE 313

1,2,3,4-Tetrahydro-6-trifluoromethyl-8-pyranono[5,6-g]quinoline (Compound **413**, structure **45A** of Scheme **XLIII**, where R^1=H, R^2=trifluoromethyl).

3-Methoxy-*trans* indanone oxime (Compound **43A**, Scheme **XLIII**). To an oven dried 250 mL rb flask equivuipped with a magnetic stir bar, a N_2 gas inlet and a water cooled reflux condenser was dissolved 7-methoxyindanone (2.0 g, 12.3 mmol), Et_3N (3.0 mL, 21.5 mmol, 1 equiv) and $NH_2OH{\cdot}HCl$ (1,48 g, 21.5 mmol, 1 equiv) in MeOH (50 mL). The clear colorless solution was heated at reflux for 12 h, cooled to rt and partially concentrated under reduced pressure to half the original volume. The liquor was diluted with H_2O (25 mL) and extracted with EtOAc (4 x 50 mL), washed with brine (3 x 25 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford 2.14 g (99%) of the desired adduct as a white solid. Data for 3-methoxy-*trans*-indanone oxime: R_f = 0.23 (hexanes/EtOAc, 3:1); ^{1}**H NMR** (400 MHz, $CDCl_3$) 8.01 (br s, 1 H), 7.47 (d, *J* = 2.4, 1 H), 6.88 (dd, *J* = 2.4, 8.3, 1 H), 6.82 (d, *J* = 8.3, 1 H), 3.30 (s, 3 H), 2.79 (m, 2 H), 2.44 (t, *J* = 6.7, 2 H).

1,2,3,4-Tetrahydro-7-methoxyquinoline (Compound **44A**, **Scheme XLIII**). In a flame dried 100 mL rb flask equivuipped with a magnetic stir bar, a N_2 gas inlet and a water cooled reflux condenser was dissolved 3-methoxy-*trans* indanone oxime (280 mg, 1.10 mmol) in dry THF. Under a blanket of N_2 the solution was cooled to 0°C and a 1.0 M solution of LAH in pentane (0.5 mL, 5.0 mmol, 4.3 equiv) was added via syringe. The solution was then heated to reflux for 4.5 h. The solution was cooled to rt and quenched with H_2O (2 mL), extracted with EtOAc (3 x 25 mL), washed with brine (50 mL), dried over Na_2SO_4 and concentrated on Celite™ to give a free flowing powder which was purified *via* flash column chromatography (silica gel, hexanes/EtOAc, 3:1) to give 14 mg (8%) of the desired adduct as an off white solid. Data for 1,2,3,4-tetrahydro-7-methoxyquinoline: $R_f = 0.35$ (hexanes/EtOAc, 3:1); ^{1}**H NMR** (400 MHz, $CDCl_3$) 6.84 (d, *J* = 8.0, 1 H), 6.19 (dd, *J* = 2.5, 8.2, 1 H), 6.03 (d, *J* = 2.5, 1 H), 3.81 (br s, 1 H), 3.73 (s, 3 H), 3.27 (m, 2 H), 2.69 (t, *J* = 6.4, 2 H), 1.91 (m, 2 H).

1,2,3,4-tetrahydro-7-hydroxyquinoline. In a flame dried 100 mL rb flask equivuipped with a magnetic stir bar and a N_2 gas inlet was dissolved 1,2,3,4-tetrahydro-7-methoxyquinoline (14.0 mg, 85.8 μmol) in CH_2Cl_2 (~3 mL). The solution was cooled to -78°C under a blanket of N_2 and a 1.0 M solution of BBr_3 in CH_2Cl_2 (0.25 mL, 250 μmol, 3 equiv) was added via syringe. The solution stirred at -78°C for 1h, warmed to 0°C for 1 h and rt for 2 h. The reaction was quenched with H2O (2 mL), extracted with CH_2Cl_2 (3 x 20 mL), washed with brine (2 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford 12 mg (88%) of the desired adduct as a yellow oil. Data for 1,2,3,4-tetrahydro-7-hydroxyquinoline: R_f = 0.21 (hexanes/EtOAc, 3:1); ^{1}**H NMR** (400 MHz, $CDCl_3$) 6.79 (d, *J* = 8.2, 1 H), 6.12 (dd, *J* = 2.4, 8.0, 1 H), 6.04 (d, *J* = 2.3, 1 H), 4.78 (br s, 1 H), 3.27 (m, 2 H), 2.67 (m, 2 H), 1.91 (m, 2 H).

1,2,3,4-Tetrahydro-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound 413, structure **45A of Scheme XLIII**, where R^1=H, R^2=trifluoromethyl). In a oven dried pressure tube equivuipped with a magnetic stir bar was dissolved 1,2,3,4-tetrahydro-7-hydroxyquinoline (11.7 mg, 78.5 μmol), TFEEA (>10 fold excess) and $ZnCl_2$ (>10 fold excess) in absolute EtOH (3 mL). The sealed pressure tube was heated at 110°C for 16 h, cooled to rt and concentrated on Celite™ to give a free flowing powder which was purified *via* flash column chromatography (silica gel, hexanes/EtOAc, 4:1) to give 8.6 mg, (41%) of Compound **413** as a bright yellow solid. Data for Compound **413**: $R_f = 0.31$ (hexanes/EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.21 (s, 1 H), 6.35 (m, 2 H), 4.66 (br s, 1 H), 3.40 (m, 2 H), 2.80 (t, *J* = 6.3, 2 H), 1.95 (m, 2 H).

EXAMPLE 314

(*R/S*)-4-Ethyl-1,2,3,4-tetrahydro-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound **414**, structure **33A** of **Scheme XL**, where $R^{1-3}=R^6=H$, R^4=ethyl, R^5=trifluoromethyl)

(*R/S*)-1-*t*-Butoxycarbonyl-4-ethyl-1,2,3,4-tetrahydro-4-hydroxy-7-methoxyquinoline. To a flame dried 250 mL r.b. flask equivuipped with a magnetic stir bar and a N_2 gas inlet was dissolved (*R/S*)-1-*t*-Butoxycarbonyl-1,2,3,4-tetrahydro-7-methoxy-4-quinolone (106 mg, 390 μmol) in dry THF (8 mL). The solution was cooled to 0°C under a blanket of N_2 and a 1.0 M solution of ethyl magnesium bromide (EtMgBr) in ethyl ether (1.3 mL, 1.36 mmol, 3.5 equiv)was added via syringe. The solution was stirred at 0°C for 2 h and at rt for 3 h. The reaction did not go to completion and starting material was observed by TLC (silica gel, hexane/EtOAc, 3:1). The reaction was quenched with H_2O (2 mL), extracted with EtOAc (4 x 25 mL), washed with brine (40 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give 38 mg (32%) of the desired alcohol as a colorless oil. Data for (*R/S*)-1-*t*-butoxycarbonyl-4-ethyl-1,2,3,4-tetrahydro-4-hydroxy-7-methoxyquinoline: $R_f = 0.14$ (hexanes/EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.36 (d, *J* = 8.7, 1 H, Ar-5H), 7.34 (d, *J* = 2.5, 1 H, Ar-8H), 6.67 (dd, *J* = 2.5, 8.5, 1 H, Ar-6H), 4.08 (m, 1 H), 3.86 (br s, 1 H, OH), 3.79 (s, 3 H, OMe), 3.43 (m, 1 H), 1.87 (m, 3 H), 1.53 (s, 9 H, t-butyl), 0.859 (t, *J* = 7.4, 3 H, -C$\underline{H}_3$).

(*R/S*)-1-*t*-Butoxycarbonyl-4-ethyl-1,2,3,4-tetrahydro-7-methoxyquinoline. To an oven dried 250 mL r.b. flask equivuipped with a magnetic stir bar and a N_2 gas inlet was dissolved (*R/S*)-1-*t*-butoxycarbonyl-4-ethyl-1,2,3,4-tetrahydro-4-hydroxy-7-methoxyquinoline (37.6 mg, 123 μmol) in dry EtOAc (8 mL). The flask was repeatedly evacuated and flushed with N_2 then a catalytic amount of 10% Pd on C (~10 mg) was added. The flask was again evacuated and flushed with N_2 several times and then H_2 was introduced by balloon. The solution was stirred under H_2 for 14 h. The flask was again evacuated and flushed with N_2 several times to remove any residual H_2 and the solution was filtered through a pad of Celite™ and concentrated *in vacuo* to give 34 mg (95%) of the desired amine as a clear colorless oil. Data for (*R/S*)-1-*t*-butoxycarbonyl-4-ethyl-1,2,3,4-tetrahydro-7-methoxyquinoline: $R_f = 0.52$ (hexanes/EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.27 (d, *J* = 2.3, 1 H, Ar-8H), 7.02 (d, *J* = 8.5, 1 H, Ar-5H), 6.59 (dd, *J* = 2.7, 8.4, 1 H, Ar-6H), 3.78 (s, 3 H, OMe), 3.74 (m, partially obscured by OMe, 1 H), 3.58 (m, 1 H), 2,62 (m, 1 H), 1.95 (m, 1 H), 1.72 (m, 2 H), 1.53 (s, 9 H, t-butyl), 1.48 (m, partially obscured by t-butyl, 1 H), 0.949 (t , *J* = 7.4, 3 H, $-CH_3$).

(*R/S*)-4-Ethyl-1,2,3,4-tetrahydro-7-methoxyquinoline. In a oven dried 250 mL r.b. flask equivuipped with a magnetic stir bar and a N_2 gas inlet was dissolved (*R/S*)-1-*t*-butoxycarbonyl-4-ethyl-1,2,3,4-tetrahydro-7-methoxyquinoline (34.0 mg, 117 µmol) in dry CH_2Cl_2 (1 mL). To the stirred solution was added TFA (1.2 mL) at rt and was allowed to react for 2 h. The dark red solution was quenched with sat $NaHCO_3$ solution (10 mL), extracted with CH_2Cl_2 (3 x 25 mL), washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford 21 mg (95%) of the desired amine as a clear light yellow oil. Data for (*R/S*)-4-ethyl-1,2,3,4-tetrahydro-7-methoxyquinoline: $R_f = 0.1$ (hexanes/EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) 6.92 (d, *J* = 8.5, 1 H), 6.21 (dd, *J* = 2.5, 8.2, 1 H), 6.03 (d, *J* = 2.5, 1 H), 3.73 (s, 3 H), 3.27 (m, 2 H), 2.59 (m, 1 H), 1.86 (m, 1 H), 1.75 (m, 2 H), 1.48 (m, 1 H), 0.968 (t, *J* = 7.4, 3 H).

(*R/S*)-4-Ethyl-1,2,3,4-tetrahydro-7-hydroxyquinoline (structure **32A** of **Scheme XL**, where R^{1-3}=H, R^4=ethyl). In a flame dried 100 mL rb flask equivuipped with a magnetic stir bar and a N_2 gas inlet was dissolved (*R/S*)-4-ethyl-1,2,3,4-tetrahydro-7-methoxyquinoline (21 mg, 109.9 µmol) in CH_2Cl_2 (4 mL). The solution was cooled to 0°C and a 1.0 M solution of BBr_3 in CH_2Cl_2 (0.33 mL, 320 µmol, 2.75 equiv) was added slowly by syringe. The solution was warmed to rt and stirred under a blanket of N_2 for 9 h. The reaction was quenched by addition of sat. $NaHCO_3$ solution (5 mL), extracted with CH_2Cl_2 (3 x 25 mL), washed with brine (2 x 20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give 19 mg (99%) of the desired phenolic amine as a clear yellow oil. Data for (*R/S*)-4-ethyl-1,2,3,4-

tetrahydro-7-hydroxyquinoline: ^{1}**H NMR** (400 MHz, $CDCl_3$) 6.85 (d, *J* = 8.1, 1 H), 6.11 (dd, *J* = 2.4, 8.3, 1 H), 5.98 (d, *J* = 2.4, 1 H), 3.25 (m, 2 H), 2.57 (m, 1 H), 1.85 (m, 1 H), 1.76 (m, 1 H), 1.67 (m, 1 H), 1.51 (m, 1 H), 0.940 (t, *J* = 7.4, 3 H).

(*R/S*)-4-Ethyl-1,2,3,4-tetrahydro-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound **414**, structure **33A** of **Scheme XL**, where R^{1-3}=R^6=H, R^4=ethyl, R^5=trifluoromethyl). In a oven dried pressure tube equivuipped with a magnetic stir bar was dissolved (*R/S*)-4-ethyl-1,2,3,4-tetrahydro-7-hydroxyquinoline (19 mg, 109 μmol) and TFEAA (excess) and $ZnCl_2$ (excess) in absolute EtOH (~3 mL). The sealed pressure tube was heated at 101°C for 10 h, cooled to rt and concentrated on Celite™ to give a free flowing powder which was purified *via* flash column chromatography (silica gel, hexanes/EtOAc, 3:1) to give 3 mg (47%) of Compound **414** as a bright yellow solid. Data for Compound **414**: R_f = 0.19 (hexanes/EtOAc, 3:1); ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.25 (s, 1 H), 6.38 (s, 1 H), 6.36 (s, 1 H), 4.70 (br s, 1 H), 3.40 (m, 2 H), 2.70 (m, 1 H), 1.89 (m, 2 H), 1.67 n(m, 1 H), 1.55 (m, 1 H), 0.95 (t, *J* = 7.4, 3 H).

EXAMPLE 315

(*R/S*)-1,2,3,4-Tetrahydro-1,4-dimethyl-8-pyranono[5,6-*g*]quinoline (Compound **415**, structure **34A** of **Scheme XL**, where R^{1-3}=R^6=R^8=H, R^4=methyl, R^5=trifluoromethyl). In a flame dried 100 mL rb flask equivuipped with a magnetic stir bar was dissolved Compound **410** (EXAMPLE 310) (10.0 mg, 35.6 μmol) in glacial acetic acid (4 mL). To the stirred solution was added *para*-formadehyde (12 mg, 356 μmol, 10 equiv). The cloudy yellow solution stirred for 10 min then $NaCNBH_3$ (12 mg, 178 μmol, 5 equiv) was added at once. Upon addition the solution emitted gas for approx 5 min then turned bright yellow. After stirring for 12 h the solution was slowly poured over ice and quenched with NaOH (20%), extracted with EtOAc (2 x 25 mL), washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give 8.9 mg (86%) of Compound **415** as a yellow-green solid. Data for Compound **415**: R_f = 0.22 (hexanes/EtOAc; 3:1); ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.25 (s, 1 H), 6.42 (s, 1 H), 6.35 (s, 1 H), 3.42 (m, 2 H), 3.00 (s, 3 H), 2.91 (m, 1 H), 2.00 (m, 1 H), 1.72 (m, 1 H), 1.28 (d, *J* = 6.8, 3 H).

EXAMPLE 316

(*R/S*)-4-Ethyl-1,2,3,4-tetrahydro-1-methyl-8-pyranono[5,6-g]quinoline (Compound **416**, structure **34A** of **Scheme XL**, where $R^{1-3}=R^6=R^8=H$, R^4=ethyl, R^5=trifluoromethyl). In a flame dried 100 mL rb flask equivuipped with a magnetic stir bar was dissolved Compound **414** (8.0 mg, 27.1 µmol) in glacial acetic acid (3 mL). To the stirred solution was added *para*-formadehyde (8.0 mg, 271 µmol, 10 equiv). The cloudy yellow solution stirred for 10 min then $NaCNBH_3$ (8.0 mg, 135 µmol, 5 equiv) was added at once. Upon addition the solution emitted gas for approx. 5 min then turned bright yellow. After stirring for 12 h the solution was slowly poured over ice and quenched with NaOH (20%), extracted with EtOAc (2 x 25 mL), washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give 7.9 mg (94% yield) of Compound **416** as a bright yellow-green solid. Data for Compound **416**: $R_f = 0.23$ (hexanes/EtOAc; 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) 7. 20 (s, 1 H), 6.43 (s, 1 H), 6.35 (s, 1 H), 3.47 (m, 1 H), 3.30 (m, 1 H), 3.00 (s, 3 H), 2.68 (m, 1 H), 1.89 (m, 2 H), 1.56 (m, 4 H), 0.980 (d, *J*= 7.4, 3 H).

EXAMPLE 317

2,2-Dimethyl-1,2,3,4-tetrahydro-6-trifloromethyl-8-pyridono[5,6-*f*]quinoline (Compound **417**, structure **40A** of **Scheme XLII**, where $R^{1-2}=R^6=H$, $R^3=R^4$=methyl, R^5=trifluoromethyl)

7-*tert*-Butyloxycarbamoyl-1,2-dihydro-2,2-dimethylquinoline (structure **36A** of **Scheme XLII**, where $R^1=R^2=H$, $R^3=R^4$=methyl). To a flame-dried 200 mL r.b. flask containing 3-*tert*-butylcarbamoylaniline (EXAMPLE 147) (7.7 g, 0.037 mol) in 40 mL of anhydrous THF was added CuCl (183 mg, 1.8 mmol), triethylamine (5.15 mL, 0.037 mol) and 3-acetoxy-3-methyl-1-butyne (4.66 g, 0.037 mol). The reaction mixture was brought to reflux for 5 h then cooled to rt and filtered though a short pad of celite. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, 7:3) afforded 6.83 g (67%) of the desired propargyl intermediate that was used directly for the next step. The propargyl amine (6.5 g, 0.0237 mol) was dissolved in 40 mL of anhydrous THF, CuCl (234 mg, 0.0024 mol) was added and the mixture was heated to reflux for 16 h. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to an oil that was subjected to chromatography (silica gel, hexanes/ethyl acetate, 9:1) which afforded 2.24 g (34%) of 7-*tert*-butyloxycarbamoyl-1,2-dihydro-2,2-dimethylquinoline along with 4.1g (63%) of the undesired regioisomer. Data for 7-*tert*-butyloxycarbamoyl-1,2-dihydro-2,2-dimethylquinoline: ^{1}**H NMR** (400 MHz, $CDCl_3$) 6.80 (bs, 1H), 6.77 (d, *J* = 7.4, 1H), 6.33 (bs, 1H), 6.31 (bd, *J* =7.4, 1H), 6.18 (d, *J* = 9.7, 1H), 5.37 (d, *J* = 9.7, 1H), 3.70 (bs, 1H), 1.49 (s, 9H), 1.27 (s, 6H).

7-Amino-1,2,3,4-tetrahydro-2,2-dimethylquinoline. A solution of 7-*tert*-butyloxycarbamoyl-1,2-dihydro-2,2-dimethylquinoline (3.4 g, 0.012 mol) in 150 mL of ethyl acetate was hydrogenated under an atmosphere of hydrogen with Pd-C 10% (340 mg) at rt for 7 h. Filtration over celite afforded 3.7 g (100%) of pure 7-*tert*-butyloxycarbamoyl-1,2,3,4-tetrahydro-2,2-dimethylquinoline. The title compound was prepared by General Method 12 (EXAMPLE 147) from 7-*tert*-butyloxycarbamoyl-1,2,3,4-tetrahydro-2,2-dimethylquinoline (3.7 g, 0.012 mol) to afford 2.35 g (100%) of 7-amino-1,2,3,4-tetrahydro-2,2-dimethylquinoline as a light reddish oil. Data for 7-amino-1,2,3,4-tetrahydro-2,2-dimethylquinoline: ^{1}**H NMR** (400 MHz, $CDCl_3$) 6.77 (d, *J* = 7.9, 1H), 6.00 (dd, *J* = 7.9, 2.2, 1H), 5.81 (d, *J* = 2.2, 1H), 3.47 (bs, 1H), 3.40 (bs, 2H), 2.66 (t, *J* = 6.7, 2H), 1.65 (t, *J* = 6.7, 2H), 1.18 (s, 6H).

2,2-Dimethyl-1,2,3,4-tetrahydro-6-trifloromethyl-8-pyridono[5,6-*f*]quinoline (Compound **417**, structure **40A** of Scheme **XLII**, where R^{1-2}=R^6=H, R^3=R^4=methyl, R^5=trifluoromethyl). This compound was prepared by General Method 13 (EXAMPLE 147) from 7-amino-1,2,3,4-tetrahydro-2,2-dimethylquinoline (2.35 g, 0.012 mol), $ZnCl_2$ (2.74 g, 0.02 mol) and ethyl 4,4,4-trifluoroacetoacetate (2.15 mL, 0.013 mol) to afford 1.91 g (48%) of Compound **417**. Data for Compound **417**: ^{1}H NMR (400 MHz, DMSO d_6) 11.70 (s, 1H), 7.18 (s, 1H), 6.85 (s, 1H), 6.35 (s, 1H), 2.65 (t, *J* = 6.6, 2H), 1.61 (t, *J* = 6.6, 2H), 1.17 (s, 6H).

EXAMPLE 318

(*R/S*)-1,2,3,4-tetrahydro-6-trifluoromethyl-2,2,4-trimethyl-8-pyridono[5,6-*f*]-3-quinolinone (Compound **418**, structure **47A** of Scheme **XLIV**, where R^1=R^2=H, R^3=trifluoromethyl)

1,9-di-*tert*-Butyloxycarbamoyl-1,2-dihydro-6-trifluoromethyl-2,2,4-trimethyl-8-pyridono[5,6-*f*]quinoline (structure **46A** of **Scheme XLIV**, where R^1=R^2=H, R^3=trifluoromethyl). To a suspension of NaH 60% in mineral oil (16 mg, 0.387 mmol) in 1 mL of anhydrous THF at 0°C, was added dropwise, a solution of Compound **247** (EXAMPLE 147) (100 mg, 0.32 mmol) and the resulting mixture was stirred at 0 °C for 10 min. A solution of t-Boc$_2$O (78 mg, 0.355 mmol) in 1 mL of THF was added dropwise and the reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with water (1 mL), extracted with ethyl acetate (2 x 5 mL) and concentrated *in vacuo* to give 148 mg (100%) of a yellow solid that was used directly for the next step. To a solution of 9-*tert*-butyloxycarbamoyl-1,2-dihydro-2,2,4-trimethyl-8-pyridono[5,6-*f*]quinoline (130 mg, 0.32mmol) in 10 mL of anhydrous THF at -78°C was added *n*-BuLi 2.5 M in hexane (121 mL, 0.32 mmol) and the mixture stirred for 10 min. t-Boc$_2$O (73 mg, 0.33 mmol) in 1 mL of THF was added and the reaction mixture stirred at -78°C for 6.5 h. The temperature was raised to 0 °C and the mixture quenched with water (3 mL), extracted with ethyl acetate (2 x 10 mL), dried (Na$_2$SO$_4$) and concentrated *in vacuo* to give a solid residue. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, 8:2) gave 79 mg (48%) of 1,9-di-*tert*-butyloxycarbamoyl-1,2-dihydro-2,2,4-trimethyl-8-pyridono[5,6-*f*]quinoline (15). **^{1}H NMR** (400 MHz, CDCl$_3$) 7.76 (s, 1H), 7.72 (s, 1H), 7.38 (s, 1H), 5.67 (s, 1H), 2.13 (s, 3H), 1.62 (s, 3H), 1.57 (s, 9H), 1.50 (s, 9H).

1-*tert*-butyloxycarbamoyl-1,2,3,4-tetrahydro-3-hydroxy-6-trifluoromethyl-2,2,4-trimethyl-8-pyridono[5,6-*f*]quinoline. A solution of 1,9-di-*tert*-butyloxycarbamoyl-1,2-dihydro-2,2,4-trimethyl-8-pyridono[5,6-*f*]quinoline (79 mg, 0.155 mmol) in 2 mL of anhydrous THF at rt was treated with 388 µL of BH$_3$.THF (1.0 M in THF, 0.388 mmol) for 3 h and was then quenched with 78 µL of NaHCO$_3$ satd't followed by 30% H$_2$O$_2$ (78 µL). The reaction mixture was stirred for 1 h, then 2 mL of water was added. The mixture was extracted with ethyl acetate (5 mL), dried (Na$_2$SO$_4$) and concentrated *in vacuo* to an oil that was subjected to flash column chromatography (silica gel, hexanes/ethyl acetate, 7:3) to give 21 mg (32%) of 1-*tert*-butyloxycarbamoyl-1,2,3,4-tetrahydro-3-hydroxy-2,2,4-trimethyl-8-pyridono[5,6-*f*]quinoline. Data for 1-*tert*-butyloxycarbamoyl-1,2,3,4-tetrahydro-3-hydroxy-2,2,4-trimethyl-8-pyridono[5,6-*f*]quinoline: **^{1}H NMR** (400 MHz, CDCl$_3$) 12.5 (bs, 1H), 7.51 (s, 1H), 7.28 (s, 1H), 6.85 (s, 1H), 3.19 (dd, *J* = 7.3, 5.2, 1H), 2.91 (m, 1H), 2.14 (d, *J* = 7.0, 1H), 1.65 (s, 3H), 1.55 (s, 9H), 1.52 (s, 3H), 1.46 (d, *J* = 6.1, 1H).

(*R/S*)-1,2,3,4-tetrahydro-6-trifluoromethyl-2,2,4-trimethyl-8-pyridono[5,6-*f*]-3-quinolinone (Compound **418**, structure **47A** of **Scheme XLIV**, where R^1=R^2=H, R^3=trifluoromethyl) To a suspension of PCC (50 mg, 0.23 mmol) in 2 mL of dichloromethane at rt was added 1-*tert*-butyloxycarbamoyl-1,2,3,4-tetrahydro-3-hydroxy-6-trifluoromethyl-2,2,4-trimethyl-8-pyridono[5,6-*f*]quinoline (16) (10 mg, 0.023 mmol) in 1 mL of dichloromethane. The reaction mixture was stirred at rt for 1.5 h, then it was filtered over celite and the solvent was removed *in vacuo* to give a dark oil that was subjected to flash column chromatography (silica gel, hexanes/ethyl acetate, 6:4) to give 5.5 mg (56%) of 1-*tert*-butyloxycarbamoyl-1,2,3,4-tetrahydro-6-trifluoromethyl-2,2,4-trimethyl-8-pyridono[5,6-*f*]-3-quinolinone that was used directly for the next step. The title compound was prepared by General Method 12 (EXAMPLE 147) from 1-*tert*-butyloxycarbamoyl-1,2,3,4-tetrahydro-6-trifluoromethyl-2,2,4-trimethyl-8-pyridono[5,6-*f*]-3-quinolinone (5.5 mg, 0.013 mmol) to afford 3 mg (71%) of Compound **418**. Data for Compound **418**: ^{1}H NMR (400 MHz, $CDCl_3$) 12.3 (bs, 1H), 7.51 (s, 1H), 6.85 (s, 1H), 6.71 (s, 1H), 4.27 (s, 1H), 3.61 (q, *J* = 6.3, 1H), 1.55 (d, *J* = 6.3, 3H), 1.40 (s, 3H), 1.31 (s, 3H).

EXAMPLE 319

5-Trifluoromethyl-7-pyridono[5,6-*e*]indoline (Compound **419**, structure **49A** of **Scheme XLV**, where R^1=trifluoromethyl, R^2=H)

6-Aminoindoline. A solution of 6-nitroindoline (1 g, 6.1 mmol) in 50 mL of ethyl acetate was hydrogenated under an atmosphere of hydrogen with Pd-C 10% (100 mg) at rt for 3 h. Filtration over celite afforded 1.0 g (98%) of 6-aminoindoline. Data for 6-aminoindoline: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.40 (d, *J* = 7.4, 1H), 6.05 (d, *J* = 2.0, 1H), 6.03 (d, *J* = 7.5, 1H), 3.67 (bs , 1H), 3.49 (t, *J* = 8.1, 2H), 3.48 (bs, 2H), 2.90 (t, *J* = 8.2, 2H).

5-Trifluoromethyl-7-pyridono[5,6-*e*]indoline (Compound **419**, structure **49A** of **Scheme XLV**, where R^1=trifluoromethyl, R^2=H) This compound was prepared by General Method 13 (EXAMPLE 147) from 6-aminoindoline (200 mg, 1.2 mmol), $ZnCl_2$ (262 mg, 1.93

mmol) and ethyl 4,4,4-trifluoroacetoacetate (194 mL, 1.32 mmol) to afford 100 mg (32%) of Compound **419**. Data for Compound **419**: ^{1}**H NMR** (400 MHz, DMSO d_6) 12.1 (s, 1H), 7.31 (s, 1H), 6.82 (s, 1H), 6.49 (s, 1H), 6.40 (s, 1H), 3.59 (t, *J* = 8.1, 2H), 3.01 (t, *J* = 8.1, 2H).

EXAMPLE 320

8-(4-Chlorobenzoyl)-5-trifluoromethyl-7-pyridono[5,6-*e*]indoline (Compound **420**, structure **50A** of **Scheme XLV**, where R^1=trifluromethyl, R^2=H, R^3=4-chlorophenyl).

To a solution of Compound **419** (EXAMPLE 319) (13 mg, 0.05 mmol) in 2 mL of anhydrous THF at -78 °C was added *n*-BuLi 2.5 M in hexane (21 mL, 0.05 mmol) and the resulting mixture was stirred for 15 min. Then 4-chlorobenzoyl chloride (6.4 mL, 0.05 mmol) was added and the reaction mixture was slowly brough to rt over a period of 30 min. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (1 mL), extracted with ethyl acetate (5 mL) and concentrated *in vacuo* to an oil that was subjected to flash column chromatography (silica gel, hexanes/ethyl acetate, 8:2) which afforded 3 mg (15%) of Compound **420**. Data for Compound **420**: ^{1}**H NMR** (400 MHz, $CDCl_3$) 8.19 (d, *J* = 8.6, 2H), 7.77 (s, 1H), 7.51 (d, *J* = 8.6, 2H), 7.25 (s, 1H), 6.99 (s, 1H), 4.45 (s, 1H), 3.77 (t, *J* = 8.0, 2H), 3.28 (t, *J* = 8.0, 2H).

EXAMPLE 321

7-*tert*-Butyloxycarbamoyl-1,2-dihydro-2,2,8-trimethylquinoline (structure **36A**, **Scheme XLII**, where R^1=R^3=R^4=methyl, R^2=H, P=*t*-butoxy, X=NH). To a flame-dried 10 mL r.b. flask containing 3-*tert*-butylcarbamoyl-2-methylaniline (EXAMPLE 155) (490 mg, 0.0022 mol) in 3 mL of anhydrous THF was added CuCl (11 mg, 0.1 mmol), triethylamine (307 mL, 0.0022 mol) and 3-acetoxy-3-methyl-1-butyne (278 mg, 0.0022 mol). The reaction mixture was brought to reflux for 5 h then cooled to rt and filtered through a short pad of celite. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, 7:3) afforded 290 mg (46%) of the desired propargyl intermediate that was used directly for the next step. The propargyl amine (290 mg, 0.001 mol) was dissolved in 5 mL of anhydrous THF, CuCl (5 mg, 0.05 mmol) was added and the mixture was heated to reflux for 16 h. The reaction mixture was diluted with ethyl acetate (10 mL), and washed with water then brine. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to an oil that was subjected to chromatography (silica gel, hexanes/ethyl acetate, 9:1) which afforded 114 mg (40%) of 7-*tert*-butyloxycarbamoyl-1,2-dihydro-2,2,8-trimethylquinoline. Data for 7-*tert*-butyloxycarbamoyl-1,2-dihydro-2,2,8-trimethylquinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) 6.85 (d, *J* = 7.4, 1H), 6.75 (d, *J* = 7.4, 1H), 6.23 (d, *J* = 9.5, 1H), 6.18 (bs, 1H), 5.42 (d, *J* = 9.5, 1H), 3.57 (bs, 1H), 1.92 (s, 3H), 1.45 (s, 9H), 1.29 (s, 6H).

7-Amino-1,2,3,4-tetrahydro-2,2,8-trimethylquinoline. A solution of 7-*tert*-butyloxycarbamoyl-1,2-dihydro-2,2,8-trimethylquinoline (114 mg, 0.39 mmol) in 4 mL of ethyl acetate was hydrogenated under an atmosphere of hydrogen with Pd-C 10% (11 mg) at rt for 7 h. Filtration over Celite afforded 60 mg (60%) of 7-*tert*-butyloxycarbamoyl-1,2,3,4-tetrahydro-2,2,8-trimethylquinoline. The title compound was prepared by General Method 12 (EXAMPLE 147) from 7-*tert*-butyloxycarbamoyl-1,2,3,4-tetrahydro-2,2,8-trimethylquinoline (60 mg, 0.206 mmol) to afford 30 mg (77%) of 7-amino-1,2,3,4-tetrahydro-2,2,8-trimethylquinoline as a light reddish oil. Data for 7-amino-1,2,3,4-tetrahydro-2,2,8-trimethylquinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) 6.70 (d, *J* = 7.9, 1H), 6.09 (d, *J* = 7.9, 1H), 3.30 (bs, 3H), 2.71 (t, *J* = 6.7, 2H), 1.89 (s, 3H), 1.65 (t, *J* = 6.7, 2H), 1.21 (s, 6H).

2,2,10-Trimethyl-1,2,3,4-tetrahydro-6-trifloromethyl-8-pyridono[5,6-*f*]quinoline (Compound **421**, structure **40A** of **Scheme XLII**, where R^1=R^3=R^4=methyl, R^2=R^6=H, R^5=trifluoromethyl). This compound was prepared by General Method 13 (EXAMPLE 147) from 7-amino-1,2,3,4-tetrahydro-2,2,8-trimethylquinoline (30 mg, 0.159 mmol), $ZnCl_2$ (35 mg, 0.255 mmol) and ethyl 4,4,4-trifluoroacetoacetate (26 mL, 0.175 mmol) to afford 21 mg (42%) of Compound **421**. Data for Compound **421**: **^{1}H NMR** (400 MHz, $CDCl_3$) 9.13 (s, 1H), 7.34 (s, 1H), 6.67 (s, 1H), 4.10 (s, 1H), 2.88 (t, *J* = 6.7, 2H), 2.10 (s, 3H), 1.75 (t, *J* = 6.7, 2H), 1.30 (s, 6H).

EXAMPLE 322

1,2,3,4-Tetrahydro-6-trifluoromethyl-8-pyridono[5,6-*f*]quinoline (Compound **422**, structure **53A** of **Scheme XLVI**, where R^{1-3}=R^5=H, R^4=trifluoromethyl)

7-Nitro-1,2,3,4-tetrahydroquinoline. 1,2,3,4-Tetrahydroquinoline (5 g, 0.0375 mol) was dissolved in 16 mL of sulfuric acid and the temperature lowered to 0°C, then 90% fuming nitric acid (1.67 mL, 0.0375 mol) was added slowly and the mixture strirred at 0°C for 30 min. It was then poured onto 100 g of ice and extracted with dichloromethane (2 x 100 mL). The organic phase was washed with saturated aqueous solution of $NaHCO_3$ (75 mL) and concentrated *in vacuo* to a reddish residue that was subjected to chromatography (silica gel, hexanes/ethyl acetate, 8:2) which afforded 4.1 g (61%) of 7-nitro-1,2,3,4-tetrahydroquinoline. Data for 7-nitro-1,2,3,4-tetrahydroquinoline: **^1H NMR** (400 MHz, $CDCl_3$) 7.39 (dd, J = 8.3, 2.2, 1H), 7.26 (d, J = 3.5, 1H), 7.01 (d, J = 8.3, 1H), 4.16 (bs, 1H), 3.35 (t, J = 5.0, 2H), 2.8 (t, J = 6.3, 2H), 1.95 (quintet, J = 6.1, 2H).

7-Amino-1,2,3,4-tetrahydroquinoline (structure **52A** of **Scheme XLVI**, where R^{1-3}=H). A solution of 7-nitro-1,2,3,4-tetrahydroquinoline (396 mg, 0.0022 mol) in 4 mL of ethyl acetate was hydrogenated under an atmosphere of hydrogen with PdC 10% (40 mg) at rt for 2 h. Filtration over celite afforded 330 mg (100%) of 7-amino-1,2,3,4-tetrahydroquinoline. Data for 7-amino-1,2,3,4-tetrahydroquinoline: **^1H NMR** (400 MHz, $CDCl_3$) 6.72 (d, J = 7.9, 1H), 6.00 (dd, J = 7.9, 2.3, 1H), 5.84 (d, J = 2.3, 1H), 3.67 (bs, 1H), 3.42 (bs, 2H), 3.24 (t, J = 5.0, 2H), 2.65 (t, J = 6.4, 2H), 1.91 (quintet, J = 6.0 Hz. 2H).

1,2,3,4-Tetrahydro-6-trifluoromethyl-8-pyridono[5,6-*f*]quinoline (Compound **422**, structure **53A** of **Scheme XLVI**, where R^{1-3}=R^5=H, R^4=trifluoromethyl) This compound was prepared by General Method 13 (EXAMPLE 147) from 7-amino-1,2,3,4-tetrahydroquinoline (330 mg, 0.0022 mol), $ZnCl_2$ (452 mg, 0.0033 mol) and ethyl 4,4,4-trifluoroacetoacetate (356 mL, 0.0024 mol) to afford 70 mg (11%) of Compound **422**. Data for Compound **422**: **^1H NMR** (400 MHz, DMSO d_6) 11.7 (bs, 1H), 7.11 (s, 1H), 6.92 (s, 1H), 6.35 (s, 2H), 3.22 (bs, 2H), 2.71 (t, J = 5.1, 2H), 1.93 (quintet, J = 6.1, 2H).

EXAMPLE 323

1,2-Dihydro-6-trifluoromethyl-1,2,2,4-tetramethyl-8-pyridono[5,6-*f*]quinoline (Compound **423**, structure **60** of **Scheme XVI**, where R^{1-2}=R^5=H, R^3=trifluoromethyl, Z=NH).

To a stirred solution of Compound **247** (EXAMPLE 147) (100 mg, 0.323 mmol) and paraformaldehyde (98 mg, 3.23 mmol) in 3 mL of acetic acid at rt was added portionwise sodium cyanoborohydride (102 mg, 1.61 mmol). The resulting mixture was stirred at 25°C for 29 h then carefully poured into 20% aqueous NaOH (10 mL) and ice 10 g and the pH adjusted to ~7. The mixture was extracted with dichloromethane (25mL), dried (Na_2SO_4) and concentrated *in vacuo* to a fluorescent yellow solid that was subjected to flash column chromatography (silica gel, hexanes/ethyl acetate, 8:2) to give 92 mg (71%) of Compound **423**. Data for Compound **423**: **^{1}H NMR** (400 MHz, $CDCl_3$) 11.21 (bs, 1H), 7.33 (s, 1H), 6.67 (s, 1H), 6.23 (s, 1H), 5.39 (s, 1H), 2.92 (s, 3H), 2.02 (s, 3H), 1.38 (s, 6H).

EXAMPLE 324

3,3-Dimethyl-5-trifluoromethyl-7-pyridono[5,6-*e*]indoline (Compound **424**, structure **57A** of **Scheme XLVII**, where R^1=methyl, R^2=R^4=H, R^3=trifluoromethyl).

2-bromo-*N*-(2-methyl-2-propenyl)-5-nitroaniline (structure **55A** of **Scheme XLVII**, where R^1=methyl, R^2=H) To a suspension of NaH 60% dispersion in oil (97 mg, 0.0023 mol) in 2 mL of anhydrous THF at 0°C was added 2-bromo-5-nitroaniline (500 mg, 0.0023 mol) in 2 mL of THF dropwise, the temperature was raised to rt to complete deprotonation then lowered to 0 °C. 3-bromo-2-methylpropene (232 mL, 0.0023 mol) was added very slowly and the reaction mixture was stirred at 0°C for 3 h then neutralized with water (5 mL). The mixture was extracted with ethyl acetate (2 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to an oil that was subjected to flash column chromatography (silica gel, hexanes/ethyl acetate, 8:2) to give 200 mg (32%) of 2-bromo-*N*-(2-methyl-2-propenyl)-5-nitroaniline (structure 55A of **Scheme XLVII**, where R^1=methyl, R^2=H). Data for 2-bromo-*N*-(2-methyl-2-propenyl)-5-nitroaniline: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.55 (d, *J* = 8.5, 1H), 7.40 (dd, *J* = 8.5, 2.8, 1H), 7.39 (d, *J* = 2.8, 1H), 4.96 (s, 2H), 4.95 (bs, 1H), 3.82 (d, *J* = 5.9, 2H), 1.81 (s, 3H).

3,3-Dimethyl-6-nitroindoline (structure **56A** of **Scheme XLVII**, where R^1=methyl, R^2=H). A solution of 2-bromo-*N*-(2-methyl-2-propenyl)-5-nitroaniline (100 mg, 0.369 mmol), $Pd(OAc)_2$ (2 mg, 0.0073 mol), Bu_4NBr (119 mg, 0.369 mmol) and triethylamine (129 mL, 0.922 mmol) in 1 mL of dry DMF under argon atmospere was heated at 80 °C for 1 h. Then sodium formate (25 mg, 0.369 mmol) was added to the reaction mixture with continued heating at 80 °C for 20 h. Water (2 mL) was added and the mixture was extracted with ethyl acetate (2 x 5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to an oil that was subjected to flash column chromatography (silica gel, hexanes/ethyl acetate, 8:2) to give 60 mg (80%) of 3,3-dimethyl-6-nitroindoline. Data for 3,3-dimethyl-6-nitroindoline: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.60 (dd, *J*= 8.2, 2.0, 1H), 7.35 (d, *J* = 2.0, 1H), 7.08 (d, *J* = 8.2, 1H), 3.98 (bs, 1H), 3.41 (s, 2H), 1.33 (s, 6H).

6-Amino-3,3-dimethylindoline. A solution of 3,3-dimethyl-6-nitroindoline (60 mg, 0.31 mmol) in 3 mL of ethyl acetate was hydrogenated under an atmosphere of hydrogen with Pd-C 10% (10 mg) at rt for 3 h. Filtration over celite afforded 45 mg (90%) of 6-amino-3,3-dimethylindoline. Data for 6-amino-3,3-dimethylindoline: **^{1}H NMR** (400 MHz, $CDCl_3$)6.80 (d, *J* = 7.8, 1H), 6.08 (dd, *J* = 7.8, 2.1, 1H), 6.01 (d, *J* = 2.1, 1H), 3.60 (bs, 1H), 3.50 (bs, 2H), 3.26 (s, 2H), 1.25 (s, 6H).

3,3-Dimethyl-5-trifluoromethyl-7-pyridono[5,6-*e*]indoline (Compound **424**, structure **57A** of **Scheme XLVII**, where R^1=methyl, R^2=R^4=H, R^3=trifluoromethyl). This compound was prepared by General Method 13 (EXAMPLE 147) from 6-amino-3,3-dimethylindoline (45 mg, 0.277 mmol), $ZnCl_2$ (57 mg, 0.416 mmol) and ethyl 4,4,4-trifluoroacetoacetate (45 mL, 0.305 mmol) to afford 7.3 mg (9%) of 3,3-dimethyl-5-trifluoromethyl-7-pyridono[5,6-*e*]indoline (22). ^{1}H NMR (400 MHz, $CDCl_3$) 12.4 (bs, 1H), 7.32 (s, 1H), 6.73 (s, 1H), 6.52 (s, 1H), 4.33 (s, 1H), 3.45 (s, 2H), 1.36 (s, 3H).

EXAMPLE 325

(*R/S*)-1,2,3,4-Tetrahydro-4-methyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (Compound **425**, structure **62A** of **Scheme XLVIII**, where R^{1-3}=R^6=H, R^4=methyl, R^5=trifluoromethyl).

1,2,3,4-Tetrahydro-4-quinolinone (structure **59A** of **Scheme XLVIII**, where R^{1-3}=H). In a 200 mL r.b. flask was introduced aniline (9.78 mL, 0.107 mol), acrylic acid (7.36 mL, 0.107 mol) and toluene (100 mL). The reaction mixture was stirred and heated at 100° C for 16 h, cooled to rt and the solvent was removed *in vacuo* to give 10.34 g (60%) of the desired intermediate carboxylic acid .that was used directly without further purification for the next step. In a 500 mL r.b. flask was introduced the acid (10.34 g, 0.064 mol) and polyphosphoric acid (200 mL). The reaction mixture was stirred and heated at 100° C for 16 h. The reaction mixture was cooled to rt, poured onto 700 mL of a 1:1 mixture of ice/water and neutralized slowly with NaOH. The aqueous phase was extracted with ethyl acetate (3 x 200 mL), dried (Na_2SO_4) and the solvent was removed *in vacuo* to give a solid residue that was subjected to flash chromatography (silica gel, hexanes/ethyl acetate, 6:1) to afford 6.97 g (76%) of 1,2,3,4-tetrahydro-4-quinolinone. Data for 1,2,3,4-tetrahydro-4-quinolinone: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.84 (dd, *J* = 7.9 , 1.1, 1H), 7.28 (ddd, *J* = 7.9, 7.9, 1.2, 1H), 6.72 (ddd, *J* = 8.1, 8.1, 0.8, 1H), 6.66 (d, *J* = 8.1, 1H), 4.49 (s, 1H), 3.56 (t, *J* = 6.9, 2H), 2.69 (t, *J* = 6.8, 2H).

1-*tert*-Butyloxycarbonyl-1,2,3,4-tetrahydro-4-quinolinone. To a stirred solution of Boc_2O (10.05 g, 0.046 mol) and 1,2,3,4-tetrahydro-4-quinolinone (6.16 g, 0.042 mol) in THF (100 mL) at 0° C was added slowly DMAP (5.11 g, 0.042 mol) in 100 mL of THF. The reaction mixture was stirred overnight, then water (75 mL) was added and the mixture was extracted with ethyl acetate (2 x 200 mL). The organic phase was dried (Na_2SO_4) and the solvent was removed *in vacuo* to give a solid residue that was subjected to flash chromatography (silica gel, hexanes/ethyl acetate, 8:2) which afforded 8.5 g (82%) of 1-*tert*-butyloxycarbamoyl-1,2,3,4-tetrahydro-4-quinolinone. Data for 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-4-quinolinone: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.98 (dd, *J* = 7.9, 1.7, 1H), 7.76 (d, *J* = 8.4, 1H), 7.49 (ddd, *J* = 7.5, 7.5, 1.7, 1H), 7.15 (ddd, *J* = 8.0, 8.0, 0.9, 1H), 4.15 (t, *J* = 6.3, 2H), 2.76 (t, *J* = 6.6, 2H), 1.55 (s, 9H).

1-*tert*-Butyloxycarbonyl-1,2,3,4-tetrahydro-4-hydroxy-4-methylquinoline. To a solution of 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-4-quinolinone (170 mg, 0.687 mmol) in THF (5 mL) at 0° C was added 3.0 M methylmagnesium bromide in ether (688 mL, 2.1 mmol). The reaction mixture was stirred at 0° C for 1 h then quenched with water (2 mL), extracted with ethyl acetate (2 x 10 mL), dried (Na_2SO_4) and the solvent was removed *in vacuo* to give an oil that was subjected to flash chromatography (silica gel, hexanes/ethyl acetate, 7:3) to afford 120 mg (66%) of 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-4-hydroxy-4-methylquinoline . Data for 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-4-hydroxy-4-

methylquinoline: ^{1}**H NMR** (400 MHz, DMSO-d_6) 7.54 (d, *J* = 7.7, 1H), 7.50 (dd, *J* = 7.7, 1.5, 1H), 7.14 (ddd, *J* = 7.3, 7.3, 1.7, 1H), 7.04 (ddd, *J* = 7.9, 7.9, 1.0, 1H), 5.14 (s, 1H), 3.69 (m, 2H), 1.87 (t, *J* = 6.5, 2H), 1.46 (s, 9H), 1.37 (s, 3H).

1-*tert*-Butyloxycarbonyl-1,2,3,4-tetrahydro-4-methylquinoline. A solution of 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-4-hydroxy-4-methylquinoline (109 mg, 0.41 mmol) in ethyl acetate (3 mL) was hydrogenated under an atmosphere of hydrogen with 10% Pd/C (10 mg) and a trace of conc. H_2SO_4 at rt for 7 h. Filtration over Celite™ afforded 93 mg (92%) of 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-4-methylquinoline. Data for 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-4-methylquinoline: ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.62 (d, *J* = 8.1, 1H), 7.16 (d, *J* = 7.8, 1H), 7.11 (ddd, *J* = 7.8, 7.8, 1.6, 1H), 7.01 (ddd, *J* = 7.7, 7.5, 1.0, 1H), 3.71 (m, 2H), 2.87 (ddq, *J* = 6.8, 6.8, 6.8, 1H), 2.04 (dddd, *J* = 7.4, 7.4, 7.4, 6.1, 1H), 1.61 (m, 1H), 1.51 (s, 9H), 1.3 (d, *J* = 6.8, 3H).

1,2,3,4-tetrahydro-4-methylquinoline (structure **60A** of **Scheme XLVIII**, where R^{1-3}=H, R^4=methyl). This compound was prepared by General Method 12 (EXAMPLE 147) from 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-4-methylquinoline (93 mg, 0.353 mmol) to afford 55 mg (95%) of 1,2,3,4-tetrahydro-4-methylquinoline as an oil which was used directly without purification for the next step.

7-Nitro-1,2,3,4-tetrahydro-4-methylquinoline. 1,2,3,4-Tetrahydro-4-methylquinoline (55 mg, 0.337 mmol) was dissolved in sulfuric acid (0.5 mL) and the temperature was lowered to 0° C. To this solution 90% fuming nitric acid (15 mL, 0.337 mmol) was added slowly and the mixture stirred at 0° C for 1 h, then warmed to rt. The reaction mixture was poured onto 1 g of ice and extracted with dichloromethane (2 x 5 mL). The organic phase was washed with sat. $NaHCO_3$ (1 x 3 mL) and concentrated *in vacuo* to a reddish residue that was subjected to chromatography (silica gel, hexanes/ethyl acetate, 8:2) which afforded 36 mg (52%) of 7-nitro-1,2,3,4-tetrahydro-4-methylquinoline. Data for 7-nitro-1,2,3,4-tetrahydro-4-methylquinoline: ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.41 (dd, *J* = 8.3, 2.2, 1H), 7.27 (d, *J* = 2.3, 1H), 7.11 (d, *J* = 8.3, 1H), 4.21 (s, 1H), 3.35 (m, 2H), 2.95 (m, 1H), 1.96 (m, 1H), 1.72 (m, 1H), 1.3 (d, *J* = 7.0, 3H).

1,2,3,4-Tetrahydro-4-methyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 425). A solution of 7-nitro-1,2,3,4-tetrahydro-4-methylquinoline (36 mg, 0.172 mmol) in ethyl acetate (3 mL) was hydrogenated under an atmosphere of hydrogen with 10% Pd/C (4 mg) at rt for 2 h. Filtration over Celite™ afforded 26 mg (85%) of 7-amino-1,2,3,4-tetrahydro-4-methylquinoline (structure **61A** of **Scheme XLVIII**, where R^{1-3}=H, R^4=methyl) that was used without further purification for the next step. The title compound was prepared by General Method 13 (EXAMPLE 147) from 7-amino-1,2,3,4-tetrahydro-4-methylquinoline (26 mg, 0.145 mmol), $ZnCl_2$ (30 mg, 0.218 mmol) and ethyl 4,4,4-trifluoroacetoacetate (21 mL, 0.145 mol) to afford 0.8 mg (2%) of 1,2,3,4-tetrahydro-4-methyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound **425**). Data for Compound **425**: **^{1}H NMR** (400 MHz, DMSO-d_6) 11.65 (bs, 1H), 7.20 (s, 1H), 6.96 (s, 1H), 6.37 (s, 2H), 3.25 (m, 2H), 2.90 (m, 1H), 1.84 (m, 1H), 1.59 (m, 1H), 1.20 (d, *J* = 6.9, 3H).

EXAMPLE 326

1,2-Dihydro-2,2,4-trimethyl-6-methoxymethyl-8-pyridono[5,6-*g*]quinoline (Compound 426, structure 57 of Scheme XVII, where R^1=R^2=H, R^3=methoxymethyl, X=NH)

To a flame-dried 25-mL rb flask at rt was added ethanol (10 mL) and 7-amino-1,2-dihydro-2,2,4-trimethylquinoline (EXAMPLE 147)(600 mg, 3.5 mmol), and the mixture stirred at rt until the amine had completely dissolved. Methyl-4-methoxyacetoacetate (680 µL, 5.3 mmol, 1.5 equiv) was then added, followed by $ZnCl_2$ (960 mg, 7.0 mmol, 2.0 equiv). The reaction was stirred at rt under N_2 for 24 h. The solvent was removed under reduced pressure, and the solid residue was dissolved in EtOAc (10 mL). The organic phase was washed with sat'd. $NaHCO_3$ (adjusted to pH 9 with 3.0 M NaOH) (3 x 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography (silica gel, CH_2Cl_2 / MeOH, 9:1), afforded 65 mg (7%) of Compound **426** as a dark yellow powder. Data for Compound **426**: R_f 0.42 (CH_2Cl_2:MeOH, 9:1); **^{1}H NMR** (400 MHz, DMSO-d_6) 11.24 (s, 1H, 9-H), 7.12 (s, 1H, 5-H), 6.63 (s, 1H, 7-H), 6.26 (s, 1H, 10-H), 6.04 (s, 1H, 3-H), 5.35 [s, 1H, $(CH_3)_2CNH$], 4.56 (s, 2H, CH_2), 3.37 (s, 3H, OCH_3), 1.93 (s, 3H, 4-CH_3), 1.21 [s, 6H, $C(CH_3)_2$].

EXAMPLE 327

1,2,2,-Trimethyl-1,2,3,4-tetrahydro-6-trifluromethyl-8-pyranono[5,6-g]quinoline (Compound **427**, structure **41A** of **Scheme XLII**, where R^{1-2}=R^6=R^8=H, R^{3-4}=methyl, R^5=trifluoromethyl).

This compound was prepared in the manner similar to that described for Compound **416** (EXAMPLE 316) from Compound **412** (EXAMPLE 312) (5 mg) to give Compound **427** (4.2 mg, 93% yield) as a bright yellow solid. Data for Compound **427**: ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.19 (s, 1 H), 6.49 (s, 1 H), 6.36 (s, 1 H), 2.91 (s, 3 H), 2.78 (t, *J* = 6.5, 2 H), 1.84 (t, *J* = 6.5, 2 H), 1.31 (s, 6 H).

EXAMPLE 328

(*R/S*)-1,2,3,4-Tetrahydro-4-propyl-6-trifluoromethyl-8-pyranono[5,6-g]quinoline (Compound **428**, structure **33A** of **Scheme XL**, where R^{1-3}, R^6=H, R^4=*n*-propyl, R^5=trifluoromethyl).

1-*tert*-Butoxycarbonyl-4-hydroxy-7-methoxy-4-propylquinoline. This compound was prepared in a manner similar to that described for 1-*tert*-butoxycarbonyl-4-ethyl-4-hydroxy-7-methoxyquinoline (EXAMPLE 314) from 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-7-methoxy-4-quinolinone (100 mg) to give the desired quinoline (51.2 mg, 40% yield) as an off-white solid. Data for 1-*tert*-butoxycarbonyl-4-hydroxy-7-methoxy-4-propyl-quinoline: ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.37 (d, *J* = 8.7, 1 H), 7.30 (d, *J* = 2.5, 1 H), 6.66 (dd, *J* = 8.9, 2.8, 1 H), 4.08 (m, 1 H), 3.86 (s, 3 H), 3.42 (m, 1 H), 2.04 (m, 1 H), 1.89 (m, 1 H), 1.81 (m, 2 H), 1.53 (s, 9 H), 1.26 (m, 2 H), 0.90 (t, *J* = 7.3, 3 H).

1-*tert*-Butoxycarbonyl-7-methoxy-4-propylquinoline. This compound was prepared in a manner similar to that described for 1-*tert*-butoxycarbonyl-4-ethyl-1,2,3,4-tetrahydro-7-methoxyquinoline (EXAMPLE 314) from 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-4-hydroxy-7-methoxy-4-propylquinoline (50 mg) to give the desired quinoline (44.3 mg, 94% yield) as a colorless oil. Data for 1-*tert*-butoxycarbonyl-7-methoxy-4-propylquinoline: ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.27 (d, *J* = 2.5, 1 H), 7.01 (d, *J* = 8.6, 1 H), 6.59 (dd, *J* = 8.5, 2.5, 1 H), 3.78 (s, 3 H), 3.73 (m, 1 H), 3.58 (m, 1 H), 2.70 (m, 1 H), 1.94 (m, 1 H), 1.71 (m, 1 H), 1.63 (m, 1 H), 1.53 (s, 9H), 1.40 (m, 3 H), 0.93 (t, *J* = 7.2, 3 H)

1,2,3,4-Tetrahydro-7-methoxy-4-propylquinoline (structure **32A** of **Scheme XL**, where R^{1-3}=H, R^4=*n*-propyl). This compound was prepared in a manner similar to that described for 4-ethyl-1,2,3,4-tetrahydro-7-methoxyquinoline (EXAMPLE 314) from 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-7-methoxy-4-propylquinoline (44 mg) to give the desired quinoline (28 mg, 98%) as a colorless oil. Data for 1,2,3,4-tetrahydro-7-methoxy-4-propylquinoline: ^{1}**H NMR** (400 MHz, $CDCl_3$) 6.90 (d, *J* = 8.2, 1 H), 6.20 (dd, *J* = 8.4, 2.6, 1 H), 6.03 (d, *J* = 2.5, 1 H), 3.83 (br s, 1 H), 3.72 (s, 3 H), 3.28 (m, 2 H), 2.68 (m, 1 H), 1.89 (m, 1 H), 1.75 (m, 1 H), 1.60 (m, 1 H), 1.46 (m, 3 H), 0.94 (t, *J* = 7.1, 3 H)

1,2,3,4-Tetrahydro-7-hydroxy-4-propylquinoline. This compound was prepared in a manner similar to that described for 4-ethyl-1,2,3,4-tetrahydro-7-hydroxyquinoline (EXAMPLE 314) from 1,2,3,4-tetrahydro-7-methoxy-4-propylquinoline (28 mg) to give the desired quinoline as a colorless oil, which was used without further purification in the following reaction. Data for 1,2,3,4-tetrahydro-7-hydroxy-4-propylquinoline: ^{1}**H NMR** (400 MHz, $CDCl_3$) 6.84 (d, *J* = 8.2, 1 H), 6.10 (dd, *J* = 8.2, 2.3, 1 H), 5.97 (d, *J* = 2.2, 1 H), 3.78 (br s, 1 H), 3.29 (m 1 H), 3.21 (m, 1 H), 2.66 (m, 1 H), 1.87 (m, 1 H), 1.75 (m, 1 H), 1.60 (m, 1 H), 1.45 (m, 3 H), 0.933 (t, *J* = 7.2, 3 H).

4-Propyl-1,2,3,4-tetrahydro-6-trifluromethyl-8-pyranono[5,6-*g*]quinoline (Compound **428**). This compound was prepared in a manner similar to that described for Compound **414** (EXAMPLE 314) from 1,2,3,4-tetrahydro-7-hydroxy-4-propylquinoline (23 mg) to give the Compound **428** (28.4 mg, 61%) as a yellow solid. Data for Compound **428**: ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.23 (s, 1 H), 6.37 (s, 1 H), 6.36 (s, 1 H), 4.70 (br s, 1 H), 3.40 (m, 2 H), 2.81 (m, 1 H), 1.88 (m, 2 H), 1.47 (m, 3 H), 0.963 (t, *J* = 7.2, 3 H)

EXAMPLE 329

1,2,3,4-Tetrahydro-2,2,4-trimethyl-6-trifluoromethyl-9-thiopyran-8-ono[5,6-*g*]quinoline (Compound **429**, structure **65A** of Scheme **XLIX**, where R^{1-2}=R^7=H, R^{3-5}=methyl, R^6=trifluoromethyl, X=S).

To a solution of Compound **266** (EXAMPLE 166) (50 mg, 0.15 mmol) in dichloromethane (7 mL) was added triethylsilane (0.23 mL , 1.5 mmol) and TFA (0.25 mL) at rt. After 15 h, the reaction was complete according to TLC. The reaction mixture was quenched with a saturated $NaHCO_3$ solution (10 mL). This solution was extracted with EtOAc (20 mL). The organic layer was washed with water and brine (3 x 5 mL each), dried (Na_2SO_4), and concentrated *in vacuo* to afford the crude product as an orange solid. The crude product was purified by prep TLC (20 x 20cm, 1000μm, 1:1 CH_2Cl_2:Hex.) to afford 49 mg (99%) of Compound **429** as a yellow solid. Data for Compound **429**: R_f = 0.44 (silica gel, 25% EtOAc:Hex); **^{1}H NMR**(400 MHz, $CDCl_3$) 7.70 (s, 1 H), 6.62 (s, 1 H), 6.46 (s, 1 H), 4.41 (brs, 1 H), 2.95 (ddq, *J* = 12.9, 6.1, 1 H), 1.81 (dd, *J* = 12.9, 1.1, 1 H), 1.48 (d, *J* = 6.1, 1 H), 1.41 (d, *J* = 6.1, 3 H), 1.31 (s, 3 H), 1.24 (s, 3 H); **IR** (film, NaCl) 1134, 1177, 1200, 1235, 1269, 1368, 1365, 1420, 1451, 1476, 1520, 1634, 3351.

EXAMPLE 330

1,2-Dihydro-1,2,2,4-tetramethyl-6-trifluoromethyl-9-thiopyran-8-ono[5,6-*g*]quinoline (Compound **430**, structure **60** of Scheme **XVI**, where R^{1-2}=R^5=H, R^3=trifluoromethyl, Z=S).

To a stirred solution of Compound **266** (EXAMPLE 166) (100 mg, 0.30 mmol) and paraformaldehyde (93 mg, 3.0 mmol) in acetic acid (3 mL) at rt was added portionwise sodium cyanoborohydride (100 mg, 1.50 mmol). The resulting mixture was stirred at rt for 16 h, then carefully poured into 20% aqueous NaOH (10 mL) and ice (10 g) and the pH adjusted to ~7. The mixture was extracted with dichloromethane (25 mL), dried (Na_2SO_4) and concentrated *in vacuo* to a fluorescent yellow solid that was subjected to flash column chromatography (silica gel, hexanes/ethyl acetate, 9:1) to give 90 mg (88%) of Compound **430** as a fluorescent yellow solid. Data for Compound **430**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.48 (s, 1 H), 6.62 (s, 1 H), 6.45 (s, 1 H), 5.40 (s, 1 H), 2.89 (s, 3 H), 2.10 (s, 3 H), 1.39 (s, 6 H).

EXAMPLE 331

1,2,3,4-Tetrahydro-1,2,2-trimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (Compound **431**, structure **41A** of Scheme **XLII**, where $R^{1-2}=R^6=R^8=H$, R^{3-4}=methyl, R^5=trifluoromethyl, X=NH).

To a stirred solution of Compound **417** (EXAMPLE 317) (21 mg, 0.07 mmol) and paraformaldehyde (22 mg, 0.70 mmol) in acetic acid (1 mL) at rt was added portionwise sodium cyanoborohydride (22 mg, 0.35 mmol). The resulting mixture was stirred at rt for 16 h then carefully poured into 20% aqueous NaOH (2 mL) and ice (10 g) and the pH adjusted to ~7. The mixture was extracted with dichloromethane (2 x 10mL), dried (Na_2SO_4) and concentrated *in vacuo* to a fluorescent yellow solid that was subjected to flash column chromatography (silica gel, hexanes/ethyl acetate, 7:3) to give 16 mg (73%) of Compound **431** as a fluorescent yellow solid. Data for Compound **431**: **^{1}H NMR** (400 MHz, $CDCl_3$) 10.83 (bs, 1 H), 7.31 (s, 1 H), 6.66 (s, 1 H), 6.29 (s, 1 H), 2.93 (s, 3 H), 2.80 (t, *J* = 6.1, 2 H), 1.83 (t, *J* = 6.5, 2 H), 1.30 (s, 6 H).

EXAMPLE 332

1,2,3,4-Tetrahydro-1-methyl-4-propyl-6-trifluoromethyl-8-pyranono[5,6-g]quinoline (Compound **432**, structure **34A** of Scheme **XL**, where $R^{1-3}=R^6=R^8=H$, R^4=*n*-propyl, R^5=trifluoromethyl).

This compound was prepared in a manner similar to that described for Compound **415** (EXAMPLE 315) from Compound **428** (EXAMPLE 328) (8.0 mg) to afford 7.9 mg (99%) of Compound **432** as a bright yellow solid. Data for Compound **432**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.18 (s, 1 H), 6.43 (s, 1 H), 6.35 (s, 1 H), 3.46 (m, 1 H), 3.33 (m, 1 H), 3.00 (s, 3 H), 1.92 (m, 1 H), 1.87 (m, 1 H), 1.49 (m, 4 H), 0.95 (d, *J* = 7.3, 3 H).

EXAMPLE 333

1,2,3,4-Tetrahydro-10-hydroxymethyl-2,2,4-trimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (Compound **433**, structure **67A** of Scheme **L**, where $R^{1-2}=R^7=H$, R^{3-5}=methyl, R^6=trifluoromethyl, X=NH).

To an oven-dried 50-mL round-bottom flask containing Compound **409** (EXAMPLE 309) (125 mg, 0.39 mmol) in 1,4-dioxane (7 mL) was added selenium dioxide (107 mg, 0.96 mmol, 2.50 equiv), and the mixture was heated to reflux for 18 h. Upon cooling to rt, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, hexanes/ethyl acetate, 4:1 to 0:1 gradient), affording 15.6 mg (12%) of Compound **433** as a fluorescent yellow solid. Data for Compound **433**: ^{1}**H NMR** (400 MHz, $CDCl_3$) 9.32 (br s, 1 H, CONH), 7.44 (s, 1 H, 5-H), 6.74 (s, 1 H, 7-H), 5.32 [br s, 1 H, $(CH_3)_2CNH$], 4.57 (d, 1 H, J = 9.7, OH), 5.02 and 4.93 (ABq, 2 H, J_{AB} = 14.0, CH_2OH), 2.85 (ddq, 1 H, J = 12.9, 12.4, 5.5, 4-H), 1.84 and 1.54 [d of ABq, 2H, J_{AB} = 13.1, J_A = 4.3, (3-H_{eq}), J_B = 0 (3-H_{ax})], 1.41 (d, 3H, J = 5.5 Hz, 4-CH_3), 1.39 and 1.26 [2s, 2 x 3H, 2-(CH_3)$_2$].

EXAMPLE 334

1,2,3,4-Tetrahydro-1,2,2,4-tetramethyl-6-trifluoromethyl-9-thiopyran-8-ono[5,6-*g*]quinoline (Compound **434**, structure **28A** of Scheme **XXXVIII**, where $R^{1-2}=R^5=H$, R^3=trifluoromethyl, Z=S)

To a solution of Compound **429** (EXAMPLE 329) (10 mg, 0..03 mmol) in acetic acid (5 mL) was added paraformaldehyde (10 mg, 0.3 mmol) and sodium cyanoborohydride (10 mg, 0.15 mmol) under nitrogen with stirring at rt. After 15 h, the reaction was complete according to ^{1}H NMR. The reaction was quenched with saturated $NaHCO_3$ (10 mL). This solution was extracted with EtOAc (20 mL). The organic layer was washed with water and brine (3 x 5 mL each), dried (Na_2SO_4), and concentrated *in vacuo* to afford the crude product. The product was purified by prep TLC (5 x 20cm, 250µm, 1:1 CH_2Cl_2:hexanes) to afford 4.5 mg (44%) of Compound **434** as a yellow solid. Data for compound **434**: ^{1}**H NMR**(400 MHz, $CDCl_3$) 7.59 (s, 1 H), 6.60 (s, 1 H), 6.53 (s, 1 H), 2.89 (s, 3 H), 2.85 (m, 1 H), 1.83 (dd, J = 13.2, 4.2, 1 H), 1.53 (d, J = 13.2, 1 H), 1.36 (d, J = 6.6, 3 H), 1.33 (s, 3 H), 1.23 (s, 3H); **IR** (film, NaCl) 1022, 1066, 1094, 1113, 1134, 1271, 1368, 1464, 1512, 1593, 2926.

EXAMPLE 335

1,2,3,4-Tetrahydro-2,2,9-trimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (Compound **435**, structure **84A** of **Scheme LVI**, where R^1=R^{5-6}=H, R^{2-3}=methyl, R^4=trifluoromethyl).

In a 25-mL r.b., a solution of Compound **417** (165 mg, 0.557 mmol) in THF (4 mL) was cooled to 0° C and treated with 60% NaH in mineral oil (23 mg, 0.58 mmol, 1.0 equivuiv). The reaction mixture was stirred 10 min. To this slurry, iodomethane (35 mL, 0.56 mmol, 1.0 equiv) was added via syringe. The reaction mixture was stirred 12 h, diluted with H_2O (20 mL), and extracted with ethyl acetate (3 x 20 mL). The extracts were washed with brine (1 x 20 mL), combined, dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (CH_2Cl_2:MeOH, 50:1) afforded 134 mg (78%) of Compound **435** as a pale yellow powder. Data for Compound **435**: **^{1}H NMR** (400 MHz, acetone-d_6): 7.35 (s, 1 H), 6.56 (s, 1 H), 6.51 (s, 1 H), 6.09 (br s, 1 H), 3.53 (s, 3 H), 2.87 (t, *J* = 6.7, 2 H), 1.76 (t, *J* = 6.7, 2 H), 1.29 (s, 6 H).

EXAMPLE 336

(*R/S*)-1,2,3,4-Tetrahydro-3-methyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (Compound **436**, structure **62A** of **Scheme XLVIII**, where R^{1-2}=R^4=R^6=H, R^3=methyl, R^5=trifluoromethyl).

1-*tert*-Butyloxycarbonyl-1,2,3,4-tetrahydro-3-methyl-4-quinolinone (structure **69A** of **Scheme LI**, where R^{1-2}=H, R^3=methyl). To a solution of 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-4-quinolinone (structure **68A** of **Scheme LI**, where R^{1-2}=H) (EXAMPLE 325) (500 mg, 0.002 mol) in THF (5 mL) at -78° C was added 2.0 M LDA in THF (1.01 mL, 0.002 mol). The reaction mixture was stirred at -78° C for 15 min and iodomethane (126 mL, 0.002 mol) was added all at once. The temperature was raised to 0° C and the resulting mixture stirred for 4 h. The reaction was then quenched with sat'd NH_4Cl (5mL), extracted with ethyl acetate (2 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to a solid residue that was subjected to flash column chromatography (silica gel, hexanes/ethyl acetate, 95:5) to give 117 mg (23%) of 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-3-methyl-4-quinolinone (structure **69A** of **Scheme LI**, where R^{1-2}=H, R^3=methyl), 128 mg (23%) of 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-3,3-dimethyl-4-quinolinone (structure **70A** of **Scheme**

LII, where R^{1-2}=H, R^{3-4}=methyl) and 200 mg (40%) of recovered starting material. Data for 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-3-methyl-4-quinolinone: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.99 (dd, *J* =7.9, 1.7, 1 H), 7.77 (d, *J* = 8.4, 1 H), 7.48 (ddd, *J* =7.3, 7.3, 1.7, 1 H), 7.13 (dd, *J* = 7.4, 1.0, 1 H), 4.32 (dd, *J* = 13.4, 4.4, 1 H), 3.69 (dd, *J* = 13.3, 9.8, 1 H), 2.76 (ddq, *J* = 9.8, 7.0, 4.4, 1 H), 1.56 (s, 9 H), 1.24 (d, *J* = 7.0, 3 H).

1-*tert*-Butyloxycarbonyl-1,2,3,4-tetrahydro-3-methylquinoline. To a solution of 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-3-methyl-4-quinolinone (117 mg, 0.45 mmol) in methanol (2 mL) at 0° C was added portionwise sodium borohydride (17 mg, 0.45 mmol) and the reaction mixture was stirred at 0° C for 3 h. The reaction was quenched with of sat'd NH_4Cl (2 mL), extracted with ethyl acetate (2 x 5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give 116 mg (98%) of the alcohol that was used directly without purification for the next step. A solution of the alcohol intermediate (116 mg, 0.44 mmol) in ethyl acetate (3 mL) was hydrogenated under an atmosphere of hydrogen with 10% Pd/C (20 mg) and a trace of conc. H_2SO_4 at rt for 16 h. Filtration over Celite™ afforded 104 mg (95%) of 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-3-methylquinoline. Data for 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-3-methylquinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.65 (d, *J* = 8.3, 1 H), 7.11 (dd, *J* = 7.7, 7.7,1 H), 7.04 (d, *J* = 7.2, 1 H), 6.96 (dd, *J* = 7.4, 7.4, 1 H), 3.97 (ddd, *J* = 12.7, 4.2, 1.0, 1 H), 3.09 (dd, *J* = 11.8, 9.8, 1 H), 2.86 (dd, *J* = 16.2, 5.3, 1 H), 2.40 (dd, *J* = 16.1, 9.6, 1 H), 2.03 (m, 1 H), 1.52 (s, 9 H), 1.05 (d, *J* = 6.7, 3 H).

1,2,3,4-tetrahydro-3-methylquinoline (structure **60A** of **Scheme LI**, where R^{1-2}=R^4=H, R^3=methyl). This compound was prepared by General Method 12 (EXAMPLE 147) from 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-3-methylquinoline (104 mg, 0.42 mmol) to afford 51 mg (83%) of 1,2,3,4-tetrahydro-3-methylquinoline as an oil which was used directly without purification for the next step.

7-Nitro-1,2,3,4-tetrahydro-3-methylquinoline. 1,2,3,4-Tetrahydro-3-methylquinoline (51 mg, 0.35 mmol) was dissolved in sulfuric acid (0.5 mL) and the temperature lowered to 0° C. To this solution 90% fuming nitric acid (15 mL, 0.35 mmol) was added slowly and the mixture stirred at 0° C for 1 h, then warmed to rt. The reaction mixture was then poured onto 1 g of ice and extracted with dichloromethane (2 x 5 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (3 mL) and concentrated *in vacuo* to a reddish residue that was subjected to chromatography (silica gel, hexanes/ethyl acetate, 85:15) which afforded 8.2 mg (12%) of 7-nitro-1,2,3,4-tetrahydro-3-methylquinoline. Data for 7-nitro-1,2,3,4-tetrahydro-3-methylquinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.39 (dd, *J* = 8.25, 2.2, 1 H), 7.27 (d, *J* = 2.3, 1 H), 7.01 (d, *J* = 8.3, 1 H), 4.19 (s, 1 H), 3.33 (m, 1 H), 2.94 (dd, *J* = 10.1, 10.1, 1 H), 2.86 (ddd, *J* = 13.8, 4.7, 1.7, 1 H), 2.46 (dd , *J* = 16.6, 10.0, 1 H), 2.05 (m, 1 H), 1.06 (d, *J* = 6.7, 3 H).

1,2,3,4-Tetrahydro-3-methyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound **436**). A solution of 7-nitro-1,2,3,4-tetrahydro-3-methylquinoline (8.2 mg, 0.042 mmol) in ethyl acetate (1 mL) was hydrogenated under an atmosphere of hydrogen with 10% Pd/C (4 mg) at rt for 2 h. Filtration over Celite™ afforded 6.2 mg (89%) of 7-amino-1,2,3,4-tetrahydro-3-methylquinoline (structure **61A** of **Scheme XLVIII**, where R^{1-2}=R^4=H, R^3=methyl) that was used without further purification for the next step. Compound **436** was prepared by General Method 13 (EXAMPLE 147) from 7-amino-1,2,3,4-tetrahydro-3-methylquinoline (6.2 mg, 0.038 mmol), $ZnCl_2$ (8.0 mg, 0.057 mmol) and ethyl 4,4,4-trifluoroacetoacetate (5.5 mL, 0.038 mol) to afford 5.8 mg (54%) of Compound **436** as a yellow solid. Data for Compound **436**: **^{1}H NMR** (400 MHz, DMSO-d6) 11.80 (bs, 1 H), 7.11 (s, 1 H), 6.95 (s, 1 H), 6.37 (s, 2 H), 3.26 (m, 1 H), 2.83 (m, 2 H), 2.51 (dd, *J* = 15.7, 10.3, 1 H), 1.88 (s, 1 H), 0.97 (d, *J* = 6.6, 3 H).

EXAMPLE 337

1,2,3,4-Tetrahydro-3,3-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound **437**, structure **73A** of **Scheme LII**, where R^{1-2}=R^5=R^7=H, R^{3-4}=methyl, R^6=trifluoromethyl).

1-*tert*-Butyloxycarbonyl-1,2,3,4-tetrahydro-3,3-dimethyl-4-quinolinone (structure **70A** of **Scheme LII**, where R^{1-2}=H, R^{3-4}=methyl). This compound was obtained along with 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-3-methyl-4-quinolinone as described above (EXAMPLE 336). Data for 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-3,3-dimethyl-4-quinolinone: **^{1}H NMR** (400 MHz, $CDCl_3$) 8.01 (dd, *J* = 7.9, 1.6, 1 H), 7.78 (d, *J* = 8.4, 1

H), 7.49 (ddd, J = 7.6, 7.6, 1.7, 1 H), 7.14 (ddd, J = 7.8, 7.8, 1.6, 1 H), 3.86 (s, 2 H), 1.56 (s, 9 H), 1.20 (s, 6 H).

1-*tert*-Butyloxycarbonyl-1,2,3,4-tetrahydro-3,3-dimethylquinoline. To a solution of 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-3,3-dimethyl-4-quinolinone (128 mg, 0.47 mmol) in methanol (2 mL) at 0° C was added portionwise sodium borohydride (18 mg, 0.47 mmol) and the reaction mixture was stirred at 0° C for 3 h. The reaction mixture was then quenched with sat'd NH_4Cl (2 mL), extracted with ethyl acetate (2 x 5 mL), dried (Na_2SO_4) and concentrated. A solution of this crude material in ethyl acetate (3 mL) was hydrogenated under an atmosphere of hydrogen with 10% Pd/C (20 mg) and a trace of conc. H_2SO_4 at rt for 16 h. Filtration over Celite™ afforded 100 mg (84%) of 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-3,3-dimethylquinoline. Data for 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-3,3-dimethylquinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.68 (d, J = 8.3, 1 H), 7.12 (ddd, J = 8.8, 8.8, 1.5, 1 H), 7.02 (d, J = 7.0, 1 H), 6.97 (ddd, J = 7.4, 7.4, 1.0, 1 H), 3.46 (s, 2 H), 2.58 (s, 2 H), 1.51 (s, 9 H), 1.01 (s, 6 H).

1,2,3,4-tetrahydro-3,3-dimethylquinoline (structure **71A** of **Scheme LII**, where R^{1-2}=R^5=H, R^{3-4}=methyl). This compound was prepared by General Method 12 (EXAMPLE 147) from 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-3,3-dimethylquinoline (100 mg, 0.38 mmol) to afford 51 mg (83%) of 1,2,3,4-tetrahydro-3,3-dimethylquinoline as an oil which was used directly without purification for the next step.

7-Nitro-1,2,3,4-tetrahydro-3,3-dimethylquinoline. 1,2,3,4-Tetrahydro-3,3-dimethylquinoline (51 mg, 0.32 mmol) was dissolved in sulfuric acid (0.5 mL) and the temperature lowered to 0° C. To this solution 90% fuming nitric acid (14 mL, 0.32 mmol) was added slowly and the mixture stirred at 0° C for 1 h, then warmed to rt. The reaction mixture was then poured onto 1 g of ice and extracted with dichloromethane (2 x 5 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (3 mL) and concentrated *in vacuo* to a reddish residue that was subjected to chromatography (silica gel, hexanes/ethyl acetate, 85:15) which afforded 39 mg (58%) of 7-nitro-1,2,3,4-tetrahydro-3,3-dimethylquinoline. Data for 7-nitro-1,2,3,4-tetrahydro-3,3-dimethylquinoline: **^{1}H NMR**

(400 MHz, $CDCl_3$) 7.40 (dd, *J* = 8.3, 2.1, 1 H), 7.29 (d, *J* = 1.8, 1 H), 7.01 (d, *J* = 8.3 H, 1 H), 4.25 (s, 1 H), 2.98 (s, 2 H), 2.54 (s, 2 H), 1.01 (s, 6 H).

1,2,3,4-Tetrahydro-3,3-dimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (Compound **437**). A solution of 7-nitro-1,2,3,4-tetrahydro-3,3-dimethylquinoline (39 mg, 0.187 mmol) in ethyl acetate (2 mL) was hydrogenated under an atmosphere of hydrogen with 10% Pd/C (4 mg) at rt for 2 h. Filtration over Celite™ afforded 30 mg (91%) of 7-amino-1,2,3,4-tetrahydro-3,3-dimethylquinoline (structure **72A** of **Scheme LII**, where R^{1-2}=R^5=H, R^{3-4}=methyl) that was used without further purification in the next step. Compound **437** was prepared by General Method 13 (EXAMPLE 147) from 7-amino-1,2,3,4-tetrahydro-3,3-dimethylquinoline (30 mg, 0.17 mmol), $ZnCl_2$ (34 mg, 025 mmol) and ethyl 4,4,4-trifluoroacetoacetate (25 mL, 0.17 mol) to afford 13 mg (26%) of Compound **437** as a yellow solid. Data for Compound **437**: **^{1}H NMR** (400 MHz, DMSO-d_6) 11.71 (bs, 1 H), 7.11 (s, 1 H), 7.01 (s, 1 H), 6.40 (s, 1 H), 6.37 (s, 1 H), 2.89 (s, 2 H), 2.51 (s, 2 H), 0.93 (s, 6 H).

EXAMPLE 338

(*R/S*)1,2,3,4-Tetrahydro-2,2,3-trimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (Compound **438**, structure **79A** of **Scheme LII**, where R^1=R^5=R^7=H, R^{2-4}=methyl, R^6=trifluoromethyl).

1-*tert*-Butoxycarbonyl-1,2,3,4-tetrahydro-2,2-dimethyl-4-quinolinone (structure **76A** of **Scheme LII**, where R^1=H, R^{2-3}=methyl). A solution of aniline (19 mL, 0.20 mol), 3-acetoxy-3-methyl-1-butyne (26 g, 0.20 mol), CuCl (1.0 g, 10 mmol) and Et_3N (28 mL, 0.20 mol) in THF (120 mL) was heated at reflux for 5 h and was filtered through a pad of Celite™. Removal of solvent and chromatography of the crude mixture (silica gel, EtOAc/hexane, 3/7) afforded 21 g (67%) of 3-methyl-3-phenylamino-1-butyne. Treatment of the aminobutyne with CuCl (0.70 mg, 7.0 mmol) in THF (200 mL) at 70° C for 16 h followed by chromatography (silica gel, EtOAc/hexane, 3/7) afforded 13 g (60%) of 1,2-dihydro-2,2-dimethylquinoline (structure **75A** of **Scheme LII**, where R^1=H, R^{2-3}=methyl). Treatment of the quinoline with di-tert-butyl dicarbonate (22 g, 0.10 mol) and DMAP (12 g, 0.10 mol) in THF (100 mL) for 16 h followed by chromatography (silica gel, EtOAc/hexane, 2/8) afforded 15 g (71%) of 1-*tert*-butoxycarbonyl-1,2-dihydro-2,2-dimethylquinoline. 1-*tert*-Butoxycarbonyl-1,2-dihydro-2,2-dimethylquinoline (3.0 g, 11 mmol) in THF (30 mL) was treated with 1.0 M BH_3-THF in THF (29 mL, 29 mmol) at rt for 3 h and was quenched with 3 M KOH (20 mL). To the above solution 30% H_2O_2 (5 mL) was added and the mixture was stirred for 60 min, then 5 mL of water was introduced. The mixture was extracted, washed with brine and concentrated. Chromatography of the crude mixture on a silica gel column using a 10-30% mixture of EtOAc/Hexane as eluents afforded a 2:1 mixture of two isomers (0.87 g, 3.1 mmol), which was oxidized with PCC (2.5 g, 11 mmol) in 60 mL of methylene chloride at rt for 60 min. Removal of solvent and chromatography of the black oil on a silica gel column using a 20% mixture of EtOAc and hexane as solvent afforded 0.58 g (68%) of 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-2,2-dimethyl-4-quinolinone as a white solid. Data for 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-2,2-dimethyl-4-quinolinone: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.93 (d, *J* = 7.8, 1 H), 7.42 (t, *J* = 7.8, 1 H), 7.31 (d, *J* = 7.8, 1 H), 7.02 (t, *J* = 7.8, 1 H), 2.73 (s, 2 H), 1.56 (s, 9 H), 1.49 (s, 6 H).

1,2,3,4-tetrahydro-2,2,3-trimethylquinoline (structure **77A** of **Scheme LII**, where R^1=R^5=H, R^{2-4}=methyl). To a solution of 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-2,2-dimethyl-4-quinolinone (0.10 g, 0.36 mmol) and iodomethane (0.50 mL , 8.0 mmol) in DMF (4 mL) was added NaH (60 % in mineral oil, 20 mg, 0.50 mmol) and the resulting mixture was stirred at rt for 2 h. The reaction was quenched with water (5 mL) and was extracted with EtOAc (2 x 15 mL). Removal of solvent and chromatography of the crude residue on a silica gel column using a 10% mixture of EtOAc and hexane as solvents afforded 90 mg (86%) of 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-2,2,3-trimethyl-4-quinolinone as a colorless oil. The oil (90 mg, 0.32 mmol) was treated with $NaBH_4$ (50 mg, 1.3 mmol) in methanol (5 mL) for 1 h and the reaction mixture was concentrated. Filtration from the inorganic material through a silica gel pad provided a colorless oil, which was then subjected to hydrogenation over 10 % Pd/C (10 mg) in EtOAc (5 mL) under a hydrogen balloon for 15 h. Filtration from the catalyst through a Celite™ pad followed by removal of solvent gave 70 mg (82%) of 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-2,2,3-trimethylquinoline as a colorless oil. The crude oil (70 mg, 0.26 mmol) was treated with

TFA (0.50 mL , 6.5 mmol) in CH_2Cl_2 for 30 min. and was quenched with 5% NaOH (6 mL). The mixture was extracted with EtOAc (2 x 15 mL) and was concentrated. Chromatography on silica gel using a 10% mixture of EtOAc and hexane afforded 1,2,3,4-tetrahydro-2,2,3-trimethylquinoline as a colorless oil (40 mg, 89%). Data for 1,2,3,4-tetrahydro-2,2,3-trimethylquinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.00-6.91 (m, 2 H), 6.60 (t, *J* = 7.3, 1 H), 6.45 (d, *J* = 7.3, 1 H), 3.61 (br s, 1 H), 2.74 (dd, *J* = 16.6, 5.3, 1 H), 2.47 (dd, *J* = 16.6, 10.3, 1 H), 1.82 (m, 1 H), 1.20 (s, 3 H), 1.05 (s, 3 H), 0.97 (d, *J* = 7.2, 3 H).

(*R/S*)1,2,3,4-Tetrahydro-2,2,3-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound **438**, structure). The quinoline (20 mg, 0.11 mmol) was converted to Compound **438** according to the nitration-hydrogenation-Knorr procedure described above for Compound **436** (EXAMPLE 336) in a 12% yield as a yellow solid (4 mg). Data for Compound **436**: **^{1}H NMR** (400 MHz, $CDCl_3$) 11.46 (s, 1 H), 7.35 (s, 1 H), 6.66 (s, 1 H), 6.31 (s, 1 H), 4.40 (s, 1 H), 2.83 (dd, *J* = 16.6, 4.8, 1 H), 2.57 (dd, *J* = 16.6, 10.3, 1 H), 1.83 (m, 1 H), 1.25 (s, 3 H), 1.10 (s, 3 H), 0.99 (d, *J* = 6.9, 3 H).

EXAMPLE 339

(*R/S-2l,4u*)-1,2,3,4-Tetrahydro-2,4-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound **439**, structure **62A** of Scheme **XLVIII**, where R^1=R^3=R^6=H, R^2=R^4=methyl, R^5=trifluoromethyl)

1-*tert*-Butoxycarbonyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinone. A mixture of aniline (3.0 g, 32 mmol) and crotonic acid (2.0 g, 23 mmol) in toluene (20 mL) was heated at reflux for 18 h. Removal of solvent and chromatography (silica gel, EtOAc/hexane, 9/1) of the crude material afforded 2.5 g (61%) of 3-phenylaminobutanoic acid. The acid was treated with PPA (20 mL) at 110° C for 6 h and the reaction mixture was poured into ice water (50 mL) and then was neutralized with Na_2CO_3 to pH 7. Extraction with EtOAc (3 x 60 mL) followed by chromatography (silica gel, EtOAc/hexane, 4/6) afforded 1.0 g (44%) of 1,2,3,4-tetrahydro-2-methyl-4-quinolinone (structure **59A** of Scheme **XLVIII**, where R^1=R^3=H, R^2=methyl) as a yellow solid. The quinolinone was treated with di-*tert*-butyl dicarbonate (2.2 g, 10 mmol) and DMAP (0.84 g, 6.8 mmol) in THF (15 mL) for 16 h followed by chromatography (silica gel, EtOAc/hexane, 2/8) to afford 1.1 g (68%) of 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinone as a yellow oil. Data for 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinone: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.99 (d, *J* = 7.5, 1 H), 7.78 (d, *J* = 7.5, 1 H), 7.50 (t, *J* = 7.5, 1 H), 7.12 (t, *J* = 7.5, 1 H), 5.10 (m, 1 H), 3.04 (dd, *J* = 17.3, 5.8, 1 H), 2.57 (dd, *J* = 17.3, 1.7, 1 H), 1.56 (s, 9 H), 1.22 (d, *J* = 6.9, 3 H).

(*R*/*S*-2*l*,4*u*)-1,2,3,4-Tetrahydro-2,4-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound **439**) To a solution of a 3.0 M ether solution of MeMgBr (1.0 mL, 3.0 mmol) was added 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinone (0.13 mg, 0.50 mmol) in THF (6 mL) and the reaction was allowed to stir at rt for 3 h, then was quenched with water (10 mL). Extraction with EtOAc (2 x 30 mL) followed by chromatography (silica gel, EtOAc/hexane, 3/7) afforded 50 mg (36%) of the adduct ,which was treated with 10% Pd/C (10 mg) and one drop of H_2SO_4 in EtOAc (15 mL) under a hydrogen atmosphere for 16 h. Filtration from the catalyst through Celite™ afforded the crude 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-2,4-dimethyl-4-quinoline, which was treated with TFA (0.4 mL) in methylene chloride (1 mL) for 30 min. The reaction was neutralized with 5 % NaOH to pH 10 and was extracted with EtOAc (2 x 20 mL). Chromatography (silica gel, EtOAc/hexane, 1/9) afforded 20 mg (69%) of (*R*/*S*-2*l*-4*u*)-1,2,3,4-tetrahydro-2,4-dimethyl-4-quinoline (structure **60A** of **Scheme LI**, where R^1=R^3=H, R^2=R^4=methyl) as a colorless oil. The quinoline was converted to the title compound according to the general nitration-hydrogenation-Knorr procedure described above for Compound **436** (EXAMPLE 336) in 14% three step yield as a yellow solid. Data for Compound **439**: **^{1}H NMR** (400 MHz, $CDCl_3$) 11.75 (s, 1 H), 7.47 (s, 1 H), 6.65 (s, 1 H), 6.33 (s, 1 H), 4.41 (s, 1 H), 3.59 (m, 1 H), 2.92 (m, 1 H), 1.94 (m, 1 H), 1.38 (d, *J* = 6.8, 3 H), 1.24 (m, 1 H), 1.22 (d, *J* = 6.4, 3 H).

EXAMPLE 340

(*R*/*S*-2*l*,4*u*)-4-Ethyl-1,2,3,4-tetrahydro-2-methyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound **440**, structure **33A** of **Scheme XL**, where R^{1-2}=R^6=H, R^3=methyl, R^4=ethyl, R^5=trifluoromethyl).

(*R/S*)-1,2,3,4-Tetrahydro-7-methoxy-2-methyl-4-quinoline. This compound was prepared in a manner similar to that described for 1,2,3,4-tetrahydro-7-methoxy-4-quinolone (EXAMPLE 310) from anisidine and crotonic acid to afford the quinolinone as a brown oil. Data for 1,2,3,4-tetrahydro-7-methoxy-2-methyl-4-quinolinone: ^{1}**HNMR** (400 MHz, $CDCl_3$) 7.78 (d, *J* = 8.7, 1 H), 6.33 (dd, *J* = 6.2, 2.2, 1 H), 6.08 (d, *J* = 2.1, 1 H), 4.27 (br s, 1 H), 3.80 (s, 3 H), 2.59 (dd, *J* = 16, 3.7, 2 H), 2.42 (dd, *J* = 13, 12, 2 H),

(*R/S*)-1-*tert*-Butoxycarbonyl-1,2,3,4-tetrahydro-7-methoxy-2-methyl-4-quinolone (structure **31A** of **Scheme XL**, where R^{1-2}=H, R^3=methyl). This compound was prepared in a manner similar to that described for 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-7-methoxy-4-quinolone (EXAMPLE 310) from 1,2,3,4-tetrahydro-7-methoxy-2-methyl-4-quinolinone (3.26 mg) to give 961 mg (62%) of the desired quinolone as an off-white solid. Data for 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-7-methoxy-2-methyl-4-quinolone: ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.94 (d, *J* = 8.9, 1 H), 7.35 (d, *J* = 2.4, 1 H), 6.67 (dd, *J* = 8.7, 2.4, 1 H), 5.08 (m, 1 H), 3.86 (s, 3 H), 2.99 (dd, *J* = 17, 5.8, 1 H), 2.48 (dd, *J* = 17, 1.7, 1 H), 1.57 (s, 9 H), 1.24 (d, *J* = 6.9, 3 H).

(*R/S*)-1-*tert*-Butoxycarbonyl-4-ethyl-1,2,3,4-tetrahydro-7-methoxy-2-methylquinoline (structure **32A** of **Scheme XL**, where R^{1-2}=H, R^3=methyl, R^4=ethyl). This compound was prepared in a manner similar to that described for 1-*tert*-butoxycarbonyl-4-ethyl-1,2,3,4-tetrahydro-7-methoxy-4-quinolone (EXAMPLE 314) from 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-7-methoxy-2-methyl-4-quinolone (100 mg) to give the desired quinoline (34 mg, 30%) as a mixture of diastereomers. Data for 1-*tert*-butoxycarbonyl-4-ethyl-1,2,3,4-tetrahydro-7-methoxy-2-methylquinoline: ^{1}**H NMR** (400 MHz, $CDCl_3$) 7.05 (d, *J* = 8.6, 1 H), 6.97 (d, *J* = 2.5, 1 H), 6.66 (dd, *J* = 8.5, 2.5, 1 H), 4.38 (m, 1 H), 3.78 (s, 3 H), 2.39 (m, 1 H), 2.28 (m, 1 H), 2.04 (m, 2 H), 1.55 (m, 1 H), 1.49 (s, 9 H),1.14 (d, *J* = 6.2, 3 H), 1.08 (t, *J* = 7.4, 3 H).

(*R/S*)-4-Ethyl-1,2,3,4-tetrahydro-7-hydroxy-2-methylquinoline. This compound was prepared in a manner similar to that described for 4-ethyl-1,2,3,4-tetrahydro-7-hydroxyquinoline (EXAMPLE 314) from 1-*tert*-butoxycarbonyl-4-ethyl-1,2,3,4-tetrahydro-

7-methoxy-2-methylquinoline (34 mg) to give the desired quinoline as a colorless oil, which was used without further purification in the following reaction.

(R/S-2l,4u)-4-Ethyl-1,2,3,4-tetrahydro-2-methyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound **440**). This compound was prepared in a manner similar to that described for Compound **414** (EXAMPLE 314) to give the desired compound as a mix of diastereomers. Recrystallization of the diastereomeric mixture afforded a sample of Compound **440**. Data for Compound **440**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.38 (s, 1 H), 6.37 (s, 1 H), 6.35 (s, 1 H), 4.43 (br s, 1 H), 3.57 (m, 1 H), 2.79 (m, 1 H), 2.04 (m, 2 H), 1.61 (m, 1 H), 1.28 (d, *J* = 6.4, 3 H), 1.00 (t, *J* = 7.3, 3 H).

EXAMPLE 341

(R/S-2l,3u)-1,2,3,4-Tetrahydro-2,3-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound **441**, structure **62A** of Scheme **XLVIII**, where R^1=R^4=R^6=H, R^{2-3}=methyl, R^5=trifluoromethyl).

To a solution of 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinone (EXAMPLE 339) (0.13 mg, 0.50 mmol) and iodomethane (0.50 mL , 8.0 mmol) in DMF (6 mL) was added NaH in a 60% mineral oil (40 mg, 1.0 mmol). The reaction mixture was stirred at rt for 16 h and was quenched by water (10 mL). Extraction of the mixture with EtOAc (2 x 30 mL) followed by chromatography (silica gel, EtOAc/hexane, 1/9) afforded a mixture of three alkylated products (125 mg, 91%). The above mixture was treated with $NaBH_4$ (38 mg, 1.0 mmol) in methanol (15 mL) for 1 h and the alcohol intermediates were purified by chromatography (silica gel, EtOAc/hexane, 3/7) to afford a mixture of three alcohols (120 mg, 95%). The mixture of alcohol intermediates (120 mg, 0.43 mmol) was treated with 10% Pd/C (20 mg) and one drop of H_2SO_4 in EtOAc (15 mL) under H_2 for 18 h. Filtration through a Celite™ pad provided the reduced products, which were directly treated with TFA (0.5 mL) in methylene chloride (1.0 m) for 1 h. The reaction was quenched with 5% NaOH, brought to pH 10, and was extracted with EtOAc (2 x 20 mL). Chromatography (silica gel, EtOAc/hexane, 2/8) afforded a mixture of three products (30 mg, 43%), containing *(R/S-2l,3u)*-1,2,3,4-tetrahydro-2,3-dimethylquinoline (structure **60A** of **Scheme LI**, where R^1=R^4=H, R^{2-3}=methyl); *(R/S-2l,3l)*-1,2,3,4-tetrahydro-2,3-

dimethylquinoline (structure **60A** of **Scheme LI**, where R^1=R^4=H, R^{2-3}=methyl), and (*R/S*)-1,2,3,4-tetrahydro-2,3,3-trimethylquinoline (structure **71A** of **Scheme LII**, where R^1=R^5=H, R^{2-4}=methyl). The mixture of the quinolines (30 mg, 0.18 mmol) was subjected to the nitration-hydrogenation-Knorr procedure described above for Compound **436** (EXAMPLE 336) to afford a mixture of Compound **441**, **442**, and **443**, which was purified by HPLC (10 mm x 25 cm ODC column, 80% MeOH/20% H_2O, 3.0 mL /min.). Data for Compound **441**: ^{1}**H NMR** (400 MHz, acetone-d_6) 10.68 (s, 1 H), 7.25 (s, 1 H), 6.48 (s, 1 H), 6.41 (s, 1 H), 6.09 (s, 1 H), 3.13 (m, 1 H), 2.80 (dd, *J* = 15.9, 4.3, 1 H), 2.53 (dd, *J* = 15.9, 12.0, 1 H), 1.61 (m, 1 H), 1.24 (d, *J* = 6.3, 3 H), 1.04 (d, *J* = 6.5, 3 H).

EXAMPLE 342

(*R/S*-2*l*,3*l*)-1,2,3,4-Tetrahydro-2,3-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound **441**, structure **62A** of **Scheme XLVIII**, where R^1=R^4=R^6=H, R^{2-3}=methyl, R^5=trifluoromethyl)

Compound **442** was obtained along with Compounds **441** and **443** as described above (EXAMPLE 341). Data for Compound 442: ^{1}**H NMR** (400 MHz, acetone-d_6) 10.80 (s, 1 H), 7.28 (s, 1 H), 6.49 (s, 1 H), 6.48 (s, 1 H), 6.15 (s, 1 H), 3.62 (m, 1 H), 2.91 (m, 1 H), 2.62 (dd, *J* = 16.3, 6.5, 1 H), 2.07 (m, 1 H), 1.15 (d, *J* = 6.5, 3 H), 0.93 (d, *J* = 6.8, 3 H).

EXAMPLE 343

(*R/S*)-1,2,3,4-Tetrahydro-2,3,3-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound **443**, structure **73A** of **Scheme LII**, where R^1=R^5=R^7=H, R^{2-4}=methyl, R^6=trifluoromethyl).

Compound **443** was obtained along with Compounds **441** and **442** as described above (EXAMPLE 341). Data for Compound **443**: ^{1}**H NMR** (400 MHz, acetone-d_6) 10.58 (s, 1 H), 7.23 (s, 1 H), 6.50 (s, 1 H), 6.41 (s, 1 H), 6.08 (s, 1 H), 3.28 (m, 1 H), 2.65 (d, *J* = 15.8, 1 H), 2.53 (d, *J* = 15.8, 1 H), 1.15 (d, *J* = 6.6, 3 H), 1.03 (s, 3 H), 0.84 (s, 3 H).

EXAMPLE 344

(*R/S*)-1,2,3,4-Tetrahydro-2-methyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound **444**, structure **53A** of **Scheme XLVI**, where R^{1-2}=R^5=H, R^3=methyl, R^4=trifluoromethyl)

1,2,3,4-tetrahydro-2-methylquinoline (0.15 g, 1.0 mmol) was converted to Compound **444** according to the nitration-hydrogenation-Knorr procedure described for Compound **436** (EXAMPLE 336) to afford 35 mg (13%) of Compound **444** as a yellow solid. Data for Compound **444**: **^{1}H NMR** (400 MHz, acetone-d_6) 10.83 (s, 1 H), 7.29 (s, 1 H), 6.55 (s, 1 H), 6.50 (s, 1 H), 6.17 (s, 1 H), 3.57 (m, 1 H), 2.91-2.82 (m, 2 H), 2.03 (m, 1 H), 1.54 (m, 1 H), 1.25 (d, *J* = 6.4, 3 H).

EXAMPLE 345

(*R/S*)-4-Ethyl-1,2,3,4-tetrahydro-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound **445**, structure **62A** of **Scheme XLVIII**, where R^{1-3}=R^6=H, R^4=ethyl, R^5=trifluoromethyl)

(*R/S*)-1-*tert*-Butyloxycarbonyl-4-ethyl-1,2,3,4-tetrahydro-4-hydroxyquinoline. To a flame-dried 25-mL rb flask containing ethylmagnesium bromide (4.0 mL of a 3.0 M solution in Et_2O, 12.0 mmol, 3.0 equiv), at -10° C was added dropwise a solution of 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-4-quinolone (1.0 g, 4.0 mmol) in Et_2O (4 mL). The reaction mixture was stirred at -10° C for 15 min, then allowed to warm to rt over 10 min. A 1.0 M solution of $NaHSO_4$ (10 mL) was then rapidly added. The resulting biphasic mixture was extracted with EtOAc (3 x 10 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexanes / EtOAc, 4:1), affording 800 mg (71%) of the desired product as a clear yellow oil (R_f 0.14, hexanes / EtOAc, 4:1). Data for 1-tert-butoxycarbonyl-4-ethyl-1,2,3,4-tetrahydro-4-hydroxyquinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.68 (d, 1H, *J* = 8.4, 8-H), 7.47 (dd, 1H, *J* = 7.9, 1.7, 5-H), 7.21 (ddd, 1H, *J* = 7.4, 7.4, 1.6, 6-H), 7.09 (ddd, 1H, *J* = 7.8, 7.8, 1.1, 7-H), 4.03 (ddd, 1H, *J* = 12.9, 7.1, 4.7, 2-H), 3.47 (ddd, 1H, *J* = 13.1, 8.6, 4.3, 2-H), 2.11 (ddd, 1H, *J* = 13.5, 8.6, 4.8, 3-H), 1.86 (m, 3H, 3-H, CH_2CH_3), 1.52 [s, 9H, $C(CH_3)_3$], 0.89 (t, 3H, *J* = 7.5, CH_3).

(*R/S*)-4-Ethyl-1,2,3,4-tetrahydroquinoline (structure **60A** of Scheme XLVIII, where R^{1-3}=H, R^4=ethyl). To a flame-dried 100-mL rb flask containing 1-*tert*-butyloxycarbonyl-4-ethyl-1,2,3,4-tetrahydro-4-hydroxyquinoline (800 mg, 2.88 mmol) in a 1:1 solution of EtOAc / EtOH (20 mL) at rt was added 10% Pd/C (approx.1 mol %). After evacuation and flushing of the vessel three times with nitrogen, one drop of trifluoroacetic acid was added, the vessel evacuated once more, and the mixture stirred under an atmosphere of hydrogen for 16 h. The reaction mixture was then filtered, and concentrated under reduced pressure. The residue was transferred to a 25-mL rb flask with CH_2Cl_2 (3 mL) and stirred at rt. TFA (1.2 mL) was added and the reaction was vented and stirred for 2 h at rt. A solution of sat'd. $NaHCO_3$ (adjusted to pH 9 with 3.0 M NaOH) was added until the aqueous phase was approximately pH 9. The resulting aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic extracts were dried (Na_2SO_4), and concentrated under reduced pressure to yield 351 mg (71%) of a colorless oil, which turned blue on exposure to air (R*f* 0.40, hexanes / EtOAc, 2:1). Data for (*R/S*)-4-ethyl-1,2,3,4-tetrahydroquinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.02 (d, 1H, *J* = 7.6, 8-H), 6.96 (ddd, 1H, *J* = 7.7, 7.7, 1.3, 7-H), 6.61 (ddd, 1H, *J* = 8.2, 8.2, 1.0, 6-H), 6.47 (d, 1H, *J* = 7.9, 5-H), 3.83 (br s, 1H, CH_2NH), 3.31 (ddd, 1H, *J* = 11.3, 11.3, 3.6, 2-H), 3.25 (ddd, 1H, *J* = 9.7, 9.7, 4.8, 2-H), 2.65 (dddd, 1H, *J* = 10.1, 5.1, 5.1, 5.1, 4-H), 1.92 (dddd, 1H, *J* = 9.6, 4.7, 4.7, 4.7, 3- H), 1.82 (m, 1H, 3-H), 1.74 (m, 1H, CH_2CH_3), 0.98 (t, 3H, *J* = 7.4, CH_3).

(*R/S*)-7-Amino-4-ethyl-1,2,3,4-tetrahydroquinoline (structure **61A** of Scheme XLVIII, where R^{1-3}=H, R^4=ethyl). A 25-mL rb flask containing (*R/S*)-4-ethyl-1,2,3,4-tetrahydroquinoline (340 mg, 2.1 mmol) was cooled to -10° C, and conc. H_2SO_4 (5 mL) was added slowly. The resulting solution was warmed to rt to effect complete dissolution of the quinoline, then cooled again to -10° C and stirred vigorously. Fuming HNO_3 (85 µL) was added dropwise, slowly, and the reaction mixture turned dark red. After 10 min, the reaction mixture was poured onto cracked ice and diluted with water (5 mL). Sat'd $NaHCO_3$ (80 mL) was added, and the pH was adjusted to pH 9 with 3.0 M NaOH. This aqueous phase was extracted with EtOAc (3 x 75 mL), and the combined extracts were dried (Na_2SO_4),and concentrated under reduced pressure to yield a dark red oil. This crude material was placed into a 250-mL rb flask with 1:1 EtOAc / EtOH (40 mL) and 10% Pd on

C (approx. 1 mol %). The vessel was evacuated and flushed with nitrogen three times, then stirred under an atmosphere of hydrogen for 16 h, filtered, and concentrated under reduced pressure to yield a yellow oil, which was purified by flash chromatography (silica gel, CH_2Cl_2 / methanol, 9:1), affording 210 mg (57 %) of the desired product as a dark yellow oil (R_f 0.50, CH_2Cl_2 / MeOH, 9:1). Data for (*R/S*)-7-amino-4-ethyl-1,2,3,4-tetrahydroquinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) 6.81 (d, 1H, *J* = 8.1, 5-H), 6.02 (dd, 1H, *J* = 8.0, 2.2, 6-H), 5.84 (d, 1H, *J* = 2.3, 8-H), 3.48 (s, 2H, NH_2), 3.27 (ddd, 1H, *J* = 11.1, 11.1, 3.5, 2-H), 3.20 (ddd, 1H, *J* = 9.8, 5.3, 4.5, 2-H), 2.55 (dddd, 1H, *J* = 10.2, 5.2, 5.2, 5.2, 4H), 1.90 (dddd, 1H, *J* = 9.6, 9.6, 9.6, 4.7, 3-H), 1.72 (m, 2H, 3-H, CH_2CH_3), 1.48 (m, 1H, CH_2CH_3), 0.96 (t, 3H, *J* = 7.4, CH_3).

(*R/S*)-4-Ethyl-1,2,3,4-tetrahydro-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound **445**). To a flame-dried 100-mL rb flask containing 7-amino-4-ethyl-1,2,3,4-tetrahydroquinoline (210 mg, 1.19 mmol), in ethanol (20 mL), at rt, was added ethyl-4,4,4-trifluoroacetoacetate (190 µL, 1.31 mmol, 1.1 equiv) followed by $ZnCl_2$ (244 mg, 1.79 mmol, 1.5 equiv). The reaction mixture was heated to reflux for 6 h, at which point all starting material had been consumed (by TLC analysis). The reaction mixture was cooled to rt, and the solvent removed under reduced pressure. Dichloromethane (20 mL) was added and the organic phase washed with sat'd $NaHCO_3$ (2 x 10 mL) and brine (1 x 10 mL), then dried (Na_2SO_4), and concentrated under reduced presure. This crude product was purified by flash chromatography (silica gel, CH_2Cl_2 / MeOH, 15:1), affording 24.4 mg (7%) of the desired product as a yellow solid. Data for Compound **445**: R_f 0.37, (CH_2Cl_2 / MeOH, 9:1); **^{1}H NMR** (400 MHz, CD_3OD) 7.31 (s, 1H, 5-H), 6.47 (s, 1H, 7-H), 6.37 (s, 1H, 10-H), 3.34 (m, 2H, 2-H), 2.70 (m, 1H, 4-H), 1.88 (m, 2H, 3-H), 1.62 (m, 2H, CH_2CH_3), 1.00 (t, 3H, *J* = 7.5, CH_3).

EXAMPLE 346

(*R/S*-2*l*, 3*u*)-1,2,3,4-Tetrahydro-2,3,9-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound **446**, structure **81A** of Scheme **LIII**, where R^1=R^4=R^6=R^8=H, R^{2-3}=methyl, R^5=trifluoromethyl)

To a solution of Compound **441** (3.5 mg, 0.012 mmol) and iodomethane (0.10 mL , 1.6 mmol) in THF (2.0 mL) was added NaH as a 60% in mineral oil (10 mg, 0.25 mmol) and the reaction was stirred at rt for 1 h, then, was quenched by water (10 mL). Extraction with EtOAc (2 x 15 mL) and chromatography (silica gel, EtOAc/hexane, 1/1) afforded 3.0 mg (81%) of Compound **446** as a yellowish solid. Data for Compound **446**: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.36 (s, 1 H), 6.72 (s, 1 H), 6.32 (s, 1 H), 4.40 (s, 1 H), 3.61 (s, 3 H), 3.14 (m, 1 H), 2.83 (dd, *J* = 16.0, 4.4, 1 H), 2.54 (dd, *J* = 16.0, 11.0, 1 H), 1.63 (m, 1 H), 1.26 (d, *J* = 6.3 , 3 H), 1.06 (d, *J* = 6.6, 3 H).

EXAMPLE 347

(*R/S*)-1,2,3,4-Tetrahydro-4-propyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (Compound **447**, structure **62A** of **Scheme XLVIII**, where R^{1-3}=R^6=H, R^4=*n*-propyl, R^5=trifluoromethyl)

1-*tert*-Butyloxycarbonyl-1,2,3,4-tetrahydro-4-hydroxy-4-propylquinoline. This compound was prepared from 1-*tert*-butyloxycarbamoyl-1,2,3,4-tetrahydro-4-quinolone (1.00 g, 4.00 mmol) in the manner previously described for 1-*tert*-butyloxycarbamoyl-4-ethyl-1,2,3,4-tetrahydro-4-hydroxyquinoline (EXAMPLE 345), affording 567 mg (48%) of the tertiary alcohol as a yellow oil (Rf 0.22, hexanes / EtOAc, 4:1). Data for 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-4-hydroxy-4-propylquinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.67 (d, 1H, *J* = 8.2, 8-H), 7.48 (dd, 1H, *J* = 7.9, 1.7, 5-H), 7.20 (ddd, 1H, *J* = 8.6, 8.6, 1.4, 6-H), 7.08 (ddd, 1H, *J* = 7.6, 7.6, 1.1, 7-H), 4.03 (ddd, 1H, *J* = 12.8, 7.1, 4.8, 2-H), 3.46 (ddd, 1H, *J* = 13.0, 8.5, 4.4, 2-H), 2.11 (ddd, 1H, *J* = 13.5, 8.5, 4.8, 3-H), 1.89 (ddd, 1H, *J* = 13.6, 7.2, 4.4, 3-H), 1.78 (m, 2H, $CH_2C_2H_5$), 1.52 [s, 9H, $C(CH_3)_3$], 1.32 (m, 2H, $CH_2CH_2CH_3$), 0.90 (t, 3H, *J* = 7.3, CH_2CH_3).

(*R/S*)-1,2,3,4-Tetrahydro-4-propylquinoline (structure **60A** of **Scheme XLVIII**, where R^{1-3}=H, R^4=*n*-propyl). This compound was prepared from 1-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-4-hydroxy-4-propylquinoline (550 mg, 1.89 mmol) in the manner previously described for 4-ethyl-1,2,3,4-tetrahydroquinoline (EXAMPLE 345), affording 229 mg (66%) of the desired tetrahydroquinoline as a yellow oil (Rf 0.10, hexanes / EtOAc, 2:1). Data for (*R/S*)-1,2,3,4-tetrahydro-4-propylquinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.07

(d, 1H, *J* = 7.6, 5-H), 7.02 (ddd, 1H, *J* = 7.9, 7.9, 1.1, 7-H), 6.77 (dd, 1H, *J* = 7.5, 7.4, 6-H), 6.67 (d, 1H, *J* = 7.9, 8-H), 6.25 (br s, 1H, N*H*), 3.37 (ddd, 1H, *J* = 11.5, 11.5, 3.5, 2-H), 3.30 (m, 1H, 2-H), 2.78 (dddd, 1H, *J* = 10.0, 5.0, 5.0, 5.0, 4-H), 1.99 and 1.84 (2 x m, 2 x 1H, 3-H), 1.68 (m, 1H, $CH_2CH_2CH_3$), 1.47 (m, 3H, $CH_2CH_2CH_3$), 0.95 (t, 3H, *J* = 7.3, CH_3).

(*R*/*S*)-7-Amino-1,2,3,4-tetrahydro-4-propylquinoline (structure **61A** of **Scheme XLVIII**, where R^{1-3}=H, R^4=*n*-propyl). This compound was prepared from (*R*/*S*)-1,2,3,4-tetrahydro-4-propylquinoline (220 mg, 0.78 mmol) in the manner previously described for 7-amino-4-ethyl-1,2,3,4-tetrahydroquinoline (EXAMPLE 345), affording 114 mg (77%) of the product as a colorless oil (Rf 0.10, hexanes / EtOAc, 2:1). Data for (*R*/*S*)-7-amino-1,2,3,4-tetrahydro-4-propylquinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) 6.80 (d, 1H, *J* = 8.0, 5-H), 6.01 (dd, 1H, *J* = 8.0, 2.3, 6-H), 5.83 (d, 1H, *J* = 2.2, 8-H), 3.74 (br s, 1H, N*H*), 3.41 (br s, 2H, NH_2), 3.28 (ddd, 1H, *J* = 11.0, 11.0, 3.3, 2-H), 3.19 (ddd, 1H, *J* = 9.7, 4.7, 4.7, 2-H), 2.65 (dddd, 1H, *J* = 5.1, 5.1, 5.1, 5.1, 4-H), 1.89 (dddd, 1H, *J* = 9.7, 9.7, 9.7, 4.5, 3-H), 1.73 (dddd, 1H, *J* = 8.6, 8.6, 4.8, 4.8, 3-H), 1.61 (m, 1H, $CH_2CH_2CH_3$), 1.40 (m, 3H, $CH_2CH_2CH_3$), 0.93 (t, 3H, *J* = 7.0, CH_3).

(*R*/*S*)-1,2,3,4-Tetrahydro-4-propyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound **447**) This compound was prepared from 7-amino-1,2,3,4-tetrahydro-4-propylquinoline (110 mg, 0.58 mmol) in the manner previously described for Compound **445** (EXAMPLE 345), affording 8.9 mg (5%) of the desired product as a yellow powder (Rf 0.44, CH_2Cl_2 / MeOH, 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.34 (s, 1H, 5-H), 6.65 (s, 1H, 7-H), 6.40 (s, 1H, 10-H), 4.65 [br s, 1H, $(CH_3)_2CNH$)], 3.42 (ddd, 1H, *J* = 11.2, 11.2, 4.0, 2-H), 3.34 (ddd, 1H, *J* = 7.9, 3.8, 3.8, 2-H), 2.82 (m, 1H, 4-H), 1.88 (m, 2H, 3-H), 1.52 (m, 4H, $CH_2CH_2CH_3$), 0.96 (t, 3H, *J* = 7.1, CH_3).

EXAMPLE 348

(*R*/*S*)-3-Ethyl-1,2,3,4-tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound **448**, structure **79A** of **Scheme LIII**, where R^1=R^5=R^7=H, R^{2-3}=methyl, R^4=ethyl, R^6=trifluoromethyl)

(*R/S*)-3-Ethyl-1,2,3,4-tetrahydro-2,2-dimethylquinoline (structure 77A of Scheme LIII, where R^1=R^5=H, R^{2-3}=methyl, R^4=ethyl). To a solution of 1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydro-2,2-dimethyl-4-quinolinone (EXAMPLE 325) (0.10 g, 0.36 mmol) and iodoethane (0.50 mL , 6.3 mmol) in DMF (5 mL) was added NaH (60 % in mineral oil, 40 mg, 1.0 mmol) and the resulting mixture was stirred at rt for 15 h. The reaction was quenched with water (5 mL) and was extracted with EtOAc (2 x 15 mL). Removal of solvent and chromatography of the crude residue on a silica gel column using a 10% mixture of EtOAc and hexane as solvents afforded a mixture of products, which was treated with TFA (0.50 mL) in methylene chloride (1.0 mL) for 3 h. The reaction was neutralized to pH 10 by 5 % NaOH and was extracted with EtOAc (2 x 20 mL). Chromatography (silica gel, EtOAc/hexane, 3/7) afforded 30 mg (41%) of (*R/S*)-3-ethyl-1,2,3,4-tetrahydro-2,2-dimethyl-4-quinolinone (30 mg, 0.15 mmol) as a colorless oil. The quinolinone (30 mg, 0.15 mmol) was treated with Et_3SiH (1.0 mL) and BF_3-OEt_2 (0.05 mL , 0.4 mmol) in CH_2Cl_2 (1.0 mL) at 100° C for 15 h in a sealed tube. Purification of the crude product by chromatography (silica gel, EtOAc/hexane, 1/9) afforded 20 mg (71%) of (*R/S*)-3-ethyl-1,2,3,4-tetrahydro-2,2-dimethylquinoline. Data for (*R/S*)-3-ethyl-1,2,3,4-tetrahydro-2,2-dimethylquinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) 6.98 (d, *J* = 7.5, 1 H), 6.96 (t, *J* = 7.5, 1 H), 6.61 (t, *J* = 7.5, 1 H), 6.44 (d, *J* = 7.5, 1 H), 3.60 (s, 1 H), 2.90 (dd, *J* = 16.7, 5.2, 1 H), 2.41 (dd, *J* = 16.7, 10.7, 1 H), 1.68 (m, 1 H), 1.52 (m, 1 H), 1.23 (m, 1 H), 1.22 (s, 3 H), 1.05 (s, 3 H).

(*R/S*)-3-Ethyl-1,2,3,4-tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 448). The quinoline prepared above (20 mg) was converted to Compound **448** according to the nitration-hydrogenation-Knorr procedure described for Compound **436** (EXAMPLE 336) to afford 2.0 mg (13%) of Compound **448** as a yellow solid. Data for Compound **448**: **^{1}H NMR** (400 MHz, acetone-d_6) 10.65 (s, 1 H), 7.31 (s, 1 H), 6.47 (s, 1 H), 6.41 (s, 1 H), 6.06 (s, 1 H), 3.01 (dd, *J* = 16.6, 4.8, 1 H), 2.53 (dd, *J* = 16.6, 11.0, 1 H), 1.72 (m, 1 H), 1.53 (m, 1 H), 1.30 (s, 1 H), 1.12 (s, 3 H), 1.10-1.00 (m, 4 H).

EXAMPLE 349

(*R/S*)-1,2,3,4-Tetrahydro-2,2-dimethyl-6-trifluoromethyl-3-propyl-8-pyridono[5,6-*g*]quinoline (Compound **449**, structure **79A** of **Scheme LIII**, where R^1=R^5=R^7=H, R^{2-3}=methyl, R^4=*n*-propyl, R^6=trifluoromethyl))

(*R/S*)-1,2,3,4-Tetrahydro-2,2-dimethyl-4-propylquinoline (structure **77A** of **Scheme LIII**, where R^1=R^5=H, R^{2-3}=methyl, R^4=*n*-propyl). This compound was prepared in a manner similar to that described for (*R/S*)-3-ethyl-1,2,3,4-tetrahydro-2,2-dimethylquinoline (EXAMPLE 348) but using iodopropane in place of iodoethane. (*R/S*)-1,2,3,4-Tetrahydro-2,2-dimethyl-4-propylquinoline was obtained in 16% overall yield as a colorless oil. Data for (*R/S*)-1,2,3,4-tetrahydro-2,2-dimethyl-4-propylquinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) 6.98 (d, *J* = 7.4, 1 H), 6.96 (t, *J* = 7.4, 1 H), 6.61 (t, *J* = 7.4, 1 H), 6.45 (d, *J* = 7.4, 1 H), 3.60 (brs, 1 H), 2.87 (dd, *J* = 16.6, 5.2, 1 H), 2.42 (dd, *J* = 16.6, 10.7, 1 H), 1.66-1.49 (m, 3 H), 1.40-1.25 (m, 2 H), 1.21 (s, 3 H), 1.05 (s, 3 H), 0.92 (t, *J* = 7.1 , 3 H).

(*R/S*)-1,2,3,4-Tetrahydro-2,2-dimethyl-6-trifluoromethyl-3-propyl-8-pyridono[5,6-*g*]quinoline (Compound **449**). Compound **449** was prepared in manner similar to that described for Compound **448** (EXAMPLE 348), to afford Compound **449** in a 32% overall yield. Data for Compound **449**: **^{1}H NMR** (400 MHz, $CDCl_3$) 11.00 (s, 1 H), 7.32 (s, 1 H), 6.61 (s, 1 H), 6.42 (s, 1 H), 4.60 (brs, 1 H), 2.90 (dd, *J* = 16.6, 4.4, 1 H), 2.45 (dd, *J* = 16.6, 11.3, 1 H), 1.70-1.42 (m, 3 H), 1.36-1.24 (m, 2 H), 1.18 (s, 3 H), 1.02 (s, 3 H), 0.93 (t, *J* = 6.7, 3 H).

EXAMPLE 350

1-Methyl-5-trifluoromethyl-7-pyridono[5,6-*f*]indoline (Compound **450**, structure **83A** of **Scheme LV**, where R^{1-3}=R^5=H, R^4=trifluoromethyl, R^6=methyl).

Compound **419** (10 mg, 0.0393 mmol) and paraformaldehyde (11 mg, 0.0393 mmol) were dissolved in glacial acetic acid (2.5 mL) and stirred for 10 min at rt. $NaBH_3CN$ (13 mg, 0.197 mmol) was added in one portion and allowed to stir at rt for 15 h. The reaction mixture was poured over ice and made basic with 10% NaOH. The aqueous layer was extracted with EtOAc (3 x 50 mL), dried (Na_2SO_4), filtered, and concentrated. The crude material was dissolved in 5% MeOH/$CHCl_3$ (0.5 mL) and loaded onto a 1000 μm reverse phase TLC plate (Whatman PLKC18F Silica Gel 150 Å). The plate was eluted with 80%

MeOH/H_2O to afford 5.8 mg (55 %) of Compound **450** as a light yellow solid. Data for Compound **450:** **^{1}H NMR** (400 MHz, acetone-d_6) 7.29 (d, *J* = 1.6, 1 H), 6.54 (s, 1 H), 6.10 (s, 1 H), 3.50 (t, *J* = 8.1, 2 H), 3.01 (t, *J* = 8.0, 2 H), 2.83 (s, 3 H).

EXAMPLE 351

6-(5-Cyano-2-thienyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound **451**, stucture 4 of **Scheme II**, where R^1=5-cyano-2-thienyl).

To a solution of 1-*tert*-butyloxycarbonyl-6-(5-formyl-2-thienyl)-1,2-dihydro-2,2,4-trimethylquinoline (12 mg, 0.03 mmol) in acetonitrile/water (10 ml/0.5 ml) was added hydroxylamine-*O*-sulphonic acid (5 mg, 0.04 mmol). The reaction mixture was heated to 65° C for 1 h. The reaction was quenched with 10% NaOH (5 mL) and extracted with EtOAc (10 mL). The organic layer was washed with water and brine (3 x 5 mL each), dried (Na_2SO_4), and concentrated *in vacuo* to afford the crude product as a yellow oil. The crude product was purified by prep. TLC (20 x 20cm, 250μm, 25% EtOAc:hexane) to afford 5 mg (40%) of 1-*tert*-butyloxycarbonyl-6-(5-cyano-2-thienyl)-1,2-dihydro-2,2,4-trimethylquinoline as a yellow oil. This product was dissolved in CH_2Cl_2 (5 mL) and treated with TFA (0.1 ml) at rt with stirring. After 2 h, the reaction was quenched with 10% NaOH (5 mL). The organic layer was washed with water and brine (3 x 5 mL each), dried (Na_2SO_4) and concentrated *in vacuo* to afford the crude product as a yellow oil. The crude product was purified by prep. TLC (20 x 20cm, 250μm, 25% EtOAc:hexane) to afford 2 mg (60%) of Compound **451** as a yellow oil. Data for Compound **451**: R_f 0.3 (silica gel, 25% EtOAc:Hex); **^{1}H NMR**(400 MHz, $CDCl_3$) 7.52 (d, *J* = 4.0, 1 H), 7.23 (s, 1 H), 7.22 (d, *J* = 7.4, 1 H), 7.07 (d, *J* = 4.0, 1 H), 6.43 (d, *J* = 7.4, 1 H), 5.38 (s, 1 H), 2.02 (s, 3 H), 1.31 (s, 6 H).

EXAMPLE 352

6-(5-Cyano-3-thienyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound **452**, stucture 4 of **Scheme II**, where R^1=5-cyano-3-thienyl).

4-Bromo-2-cyanothiophene. To a solution of 4-bromo-2-thiophenecarboxaldehyde (1.0 g, 5.2 mmol, Aldrich) in acetonitrile/water (20 mL/2 mL) was added hyroxylamine-*O*-sulfonic acid (2.4 g, 21.2 mmol, Aldrich). The dark solution was heated to 65° C with stirring. After

8 h, the reaction was quenched with 10% NaOH (10 mL). The solution was extracted with EtOAc (30 mL). The organic layer was washed with water and brine (3 x 10 mL each), dried (Na_2SO_4), and concentrated *in vacuo* to afford the crude product as a tan solid. The crude product was purified by silica flash chromatography (5-25% EtOAc:hexane) to afford 0.50 g (51%) of 4-bromo-2-cyanothiophene as a white solid. Data for 4-bromo-2-cyanothiophene: Rf 0.49 (silica, 25% EtOAc:hex.); **^{1}H NMR**(400 MHz, $CDCl_3$) 7.54 (s, 1 H), 7.50 (s, 1 H).

6-(5-Cyano-3-thienyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound **452**). This compound was prepared by General Method 2 from compound **9** (200 mg, 0.63 mmol) and 4-bromo-2-cyanothiophene (0.50 g, 2.65 mmol). The crude product was purified by prep. TLC (20 x 20cm, 1000μm, 25% ETOAc:Hexane) to afford 160 mg (91%) of Compound **452** as a yellow oil. Data for Compound **452**: R*f* 0.50 (silica gel, 25% EtOAc:hex); **^{1}H NMR**(400 MHz, $CDCl_3$) 7.79 (s, 1 H), 7.46 (s, 1 H), 7.20 (s, 1 H), 7.16 (d, *J* = 8.3, 1 H), 6.46 (d, *J* = 8.3, 1 H), 5.37 (s, 1 H), 2.03 (s, 3 H), 1.31 (s, 6 H); **IR** (film, NaCl) 1159, 1381, 1402, 1449, 1476, 1499, 1609, 1653, 2216, 2915, 3294, 3584.

EXAMPLE 353

6-(3-Formylphenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound **453**, structure **4** of Scheme **II**, where R^1=3-formylphenyl)

This compound was prepared by General Method 2 from Compound **9** (50 mg, 0.158 mmol) and 2-(3-bromophenyl)-1,3-dioxolane (171 mg, 0.788 mmol). Purification by flash chromatography on silica gel (20 g) using 5% EtOAc:hexanes afforded 21 mg (48%) of Compound **453** as a yellow oil. Data for Compound **453**: **^{1}H NMR** (400 MHz, acetone-d_6) 10.09 (s, 1 H), 8.11 (d, *J* = 1.4, 1 H), 7.90 (d, *J* = 7.2, 1 H), 7.77 (d, *J* = 7.5, 1 H), 7.59 (t, *J* = 7.6, 1 H), 7.40 (d, *J* = 2.2, 1 H), 7.33 (dd, *J* = 8.4, 2.2, 1 H), 6.61 (d, *J* = 8.2, 1 H), 5.40 (s, 1 H), 5.38 (bs, 1 H), 1.29 (s, 9 H).

EXAMPLE 354

1,2-Dihydro-2,2,4-trimethyl-6-[3-(methylsulfonyl)phenyl]quinoline (Compound **454**, structure **4** of Scheme **II**, where R^1=3-(methylsulfonyl)phenyl)

3-Bromophenyl(methyl)sulfone. In a 50 mL r.b flask, *m*-CPBA (623 mg, 2.166 mmol, 60%) was suspended in CH_2Cl_2 (20 mL) and cooled to -20° C. 3-Bromothioanisole (200 mg, 0.985 mmol) in CH_2Cl_2 (1 mL) was added to the slurry and allowed to warm to rt for 2 h. The reaction was quenched with H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were washed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated onto Celite™. The material was purified by flash chromatography on silica gel (40 g) using 30% EtOAc/hexanes as eluent to afford 229 mg (99 %) of the sulfone as a tan solid. Data for 3-bromophenyl(methyl)sulfone: **^{1}H NMR** (400 MHz, $CDCl_3$) 8.10 (t, *J* = 1.6, 1 H), 7.88 (d, *J* = 7.9, 1 H), 7.79 (d, *J* = 8.0, 1 H), 7.46 (t, *J* = 7.9, 1 H), 3.07 (s, 3 H).

1,2-Dihydro-2,2,4-trimethyl6-[3-(methylsulfonyl)phenyl]quinoline (Compound **454**). This compound was prepared by a modification of General Method 2 as follows. A flask was charged with Compound **9** (123 mg, 0.388 mmol), the sulfone (83 mg, 0.353 mmol), $Pd(OAc)_2$ (4 mg, 0.018 mmol), triphenylphosphine (18.5 mg, 0.071 mmol), and K_3PO_4 (112.4 mg, 0.530 mmol). The flask was flushed with N_2 for 5 min and then 5 mL of DMF (anhydrous) was added. The resulting reaction mixture was heated to 100° C for 15 h. The reaction was allowed to cool to rt and was quenched with H_2O (20 mL). The aqueous layer was extracted with EtOAc (3x100 mL). The combined organics were washed with H_2O (3x50 mL) and brine (30 mL), dried (Na_2SO_4), filtered and concentrated. The resulting material was dissolved in dimethylsulfide (0.5 mL), and cooled to 0° C. This solution was treated with trifluoroacetic acid (0.5 mL) and allowed to stir at 0° C for 1h. The reaction was quenched with H_2O (2 mL) followed by a slow addition of $NaHCO_3$ (sat) until neutralized. The aqueous was extracted with EtOAc (2 x 30 mL). The combined organics were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated onto Celite™. The material was purified by flash chromatography on silica gel (30 g) using 25% EtOAc/hexanes as eluent to give 15 mg (12% overall) of Compound **454** as a light yellow film. Data for Compound **454**: **^{1}H NMR** (400 MHz, acetone-d_6) 8.08 (t, *J* = 1.8, 1 H), 7.91 (dd, *J* = 6.7, 1.5, 1 H), 7.78 (dd, *J* = 6.5, 1.6, 1 H), 7.64 (t, *J* = 7.8, 1 H), 7.39 (d, *J* = 2.1, 1 H), 7.33 (dd, *J* = 8.1, 2.0, 1 H), 6.61 (d, *J* = 8.1, 1 H), 5.43 (bs, 1 H), 5.41 (s, 1 H), 3.16 (s, 3 H), 2.09 (s, 3 H), 1.3 (s, 6 H).

EXAMPLE 355

(*R/S*)-6-(3-Cyano-5-fluorophenyl)-1,2,3,4-Tetrahydro-2,2,4-trimethylquinoline (Compound 455, structure **5** of **Scheme I**, where R^1=3-cyano-5-fluorophenyl)

A 25 mL r.b. flask was charged with Compound **271** (EXAMPLE 171) (145.0 mg, 0.50 mmol), ethyl acetate (1 mL) and 10% Pd/C (10 mg). The flask was fitted with a septum and the system was flushed with nitrogen. A balloon filled with hydrogen gas was inserted into the reaction flask and the reaction was allowed to progress at rt for 2 h. The crude reaction mixture was filtered through a plug of Celite™. The crude mixture was purified by reverse phase semi-preparatory HPLC (70 % methanol/water-with trace triethyl amine; retention time 29 min.) yielding 50.0 mg (34%) of Compound **455**. Data for Compound **455**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.81 (dt, *J* = 2.9, 1.5, 1 H), 7.65 (ddt, *J* = 8.9, 3.7, 2.3, 1 H), 7.55 (s, 1 H), 7.37 (dd, *J* = 9.7, 1.1, 1 H), 7.32 (dd, *J* = 8.6, 1.2, 1 H), 6.59 (d, *J* = 8.4, 1 H), 5.25 (br s, 1 H), 2.95 (m, 1 H), 1.80 (ddd, *J* = 8.0, 5.4, 1.5, 1 H), 1.40 (m, 4 H), 1.25 (s, 3 H), 1.19 (s, 3 H).

EXAMPLE 356

(*R/S*)-9-Chloro-1,2-dihydro-2,2,4-trimethyl-5-phenyl-5*H*-chromeno[3,4-*f*]quinoline (Compound **456**, structure **42** of **Scheme XI**, where R=phenyl R^1=H, R^2=Cl)

This compound was prepared by General Method 5 (Example 60) from Compound **209** (75 mg, 0.230 mmol) and phenyl magnesium bromide (1.84 mL, 1.84 mmol) to afford 61 mg (68 %) of Compound **456** as a clear film. Data for Compound **456**: **^{1}H NMR** (400 MHz, acetone-d_6) 7.58 (d, *J* = 2.3, 1 H), 7.56 (s, 1 H), 7.22 (m, 4 H), 7.19 (m, 1 H), 6.94 (dd, *J* = 8.5, 2.5, 2 H), 6.83 (d, *J* = 8.5, 1 H), 6.76 (d, *J* = 8.5, 1 H), 5.63 (br s, 1 H), 5.46 (d, *J* = 8.5, 1 H), 1.98 (s, 3 H), 1.26 (s, 3 H), 1.24 (s, 3 H).

EXAMPLE 357

(*R/S*)-5-Butyl-1,2-dihydro-2,2,4,9-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 457, structure **42** of **Scheme XI**, where R=*n*-butyl, R^1=H, R^2=methyl).

This compound was prepared by General Method 5 (EXAMPLE 60) from Compound **316** (EXAMPLE 216) (44 mg, 0.14 mmol) and *n*-BuLi (2.5 M in hexanes, 0.30 mL, 0.75 mmol, 5.2 equivuiv) to afford 12 mg (24%) of Compound **457** as a pale yellow glass. Data for Compound **457**: **^{1}H NMR** (400 MHz, acetone-d$_6$): 7.48 (s, 1 H), 7.45 (d, J = 8.2, 1 H), 6.91 (d, J = 6.6, 1 H), 6.76 (d, J = 8.0, 1 H), 6.67 (d, J = 8.2, 1H), 5.80 (dd, J = 7.9, 3.3, 1 H), 5.51 (s, 1 H), 5.36 (br s, 1 H), 2.81 (s, 3 H), 2.78 (s, 3 H), 1. 75 (m, 1 H), 1.55-1.35 (m, 3 H), 1.30-1.20 (m, 2 H), 1.27 (s, 3 H), 1.18 (s, 3 H), 0.84 (t, J = 7.3, 3 H).

Steroid Receptor Activity

Utilizing the "cis-trans" or "co-transfection" assay described by Evans et al., Science, 240:889-95 (May 13, 1988), the disclosure of which is herein incorporated by reference, the compounds of the present invention were tested and found to have strong, specific activity as both agonists, partial agonists and antagonists of PR, AR, ER, GR and MR. This assay is described in further detail in U.S. Patent Nos. 4,981,784 and 5,071,773, the disclosures of which are incorporated herein by reference.

The co-transfection assay provides a method for identifying functional agonists and partial agonists which mimic, or antagonists which inhibit, the effect of native hormones, and quantifying their activity for responsive IR proteins. In this regard, the co-transfection assay mimics an *in vivo* system in the laboratory. Importantly, activity in the co-transfection assay correlates very well with known *in vivo* activity, such that the co-transfection assay functions as a qualitative and quantitative predictor of a tested compounds *in vivo* pharmacology. See, e.g., T. Berger et al. 41 *J. Steroid Biochem. Molec. Biol.* 773 (1992), the disclosure of which is herein incorporated by reference.

In the co-transfection assay, a cloned cDNA for an IR (e.g., human PR, AR or GR) under the control of a constitutive promoter (e.g., the SV 40 promoter) is introduced by transfection (a procedure to induce cells to take up foreign genes) into a background cell substantially devoid of endogenous IRs. This introduced gene directs the recipient cells to make the IR protein of interest. A second gene is also introduced (co-transfected) into the same cells in conjunction with the IR gene. This second gene, comprising the cDNA for a reporter protein, such as firefly luciferase (LUC), controlled by an appropriate hormone responsive promoter containing a hormone response element (HRE). This reporter plasmid functions as a reporter for the transcription-modulating activity of the target IR. Thus, the reporter acts as a surrogate for the products (mRNA then protein) normally expressed by a gene under control of the target receptor and its native hormone.

The co-transfection assay can detect small molecule agonists or antagonists of target IRs. Exposing the transfected cells to an agonist ligand compound increases reporter activity in the transfected cells. This activity can be conveniently measured, e.g., by increasing luciferase production, which reflects compound-dependent, IR-mediated increases in reporter transcription. To detect antagonists, the co-transfection assay is carried out in the presence of a constant concentration of an agonist to the target IR (e.g., progesterone for PR) known to induce a defined reporter signal. Increasing concentrations of a suspected antagonist will decrease the reporter signal (e.g., luciferase production). The co-transfection assay is therefore useful to detect both agonists and antagonists of specific IRs. Furthermore, it determines not only whether a compound interacts with a particular IR, but whether this interaction mimics (agonizes) or blocks (antagonizes) the effects of the native regulatory molecules on target gene expression, as well as the specificity and strength of this interaction.

The activity of selected steroid receptor modulator compounds of the present invention were evaluated utilizing the co-transfection assay, and in standard IR binding assays, according to the following illustrative Examples.

EXAMPLE 358

Co-transfection assay

CV-1 cells (African green monkey kidney fribroblasts) were cultured in the presence of Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% charcoal resin-stripped fetal bovine serum then transferred to 96-well microtiter plates one day prior to transfection.

To determine PR agonist and antagonist activity of the compounds of the present invention, the CV-1 cells were transiently transfected by calcium phosphate coprecipitation according to the procedure of Berger et al., 41 *J. Steroid Biochem. Mol. Biol.*, 733 (1992) with the following plasmids: pSVhPR-B (5 ng/well), MTV-LUC reporter (100 ng/well), pRS-ß-Gal (50 ng/well) and filler DNA (pGEM; 45 ng/well). The receptor plasmid, pSVhPR-B, contains the human PR-B under constitutive control of the SV-40 promoter, and is more fully described in E. Vegeto et al., "The mechanism of RU 486 antagonism is dependent on the conformation of the carboxy-terminal tail of the human progesterone receptor", 69 *Cell*, 703 (1992), the disclosure of which is herein incorporated by reference. Similarly, the AR, ER, GR and MR agonist and antagonist activity of the compounds of the present invention were determined according to the same procedure described herein, except that the plasmids pRShAR, pRShER, pRShGR and pRShMR were substituted for the plasmid pSVhPR-B described above. Each of these plasmids are more fully described in J.A. Simental et al., "Transcriptional activation and nuclear targeting signals of the human androgen receptor", 266 *J. Biol. Chem.*, 510 (1991) (pRShAR), M.T. Tzukerman et al., "Human estrogen receptor transactivational capacity is determined by both cellular and promoter context and mediated by two functionally distinct intramolecular regions", 8 *Mol. Endocrinol.*, 21 (1994) (pRShER), V. Giguere et al., "Functional domains of the human glucocorticoid receptor", 46 *Cell*, 645 (1986) (pRShGR), and J.L. Arriza et al., "Cloning of human mineralocorticoid receptor complementary DNA: structural and functional kinship with glucocorticoid receptor", 237 *Science*, 268 (1987) (pRShMR), the disclosures of which are herein incorporated by reference.

The reporter plasmid, MTV-LUC, contains the cDNA for firefly luciferase (LUC) under control of the mouse mammary tumor virus (MTV) long terminal repeat, a conditional promoter containing a progesterone response element. This plasmid is more fully described in Berger et al. supra. In addition, for ER agonist and antagonist determinations, the reporter plasmid MTV-ERE5-LUC, which contains LUC under control of the mouse mammary tumor virus (MTV) long terminal repeat in which the glucocorticoid response elements have been deleted and replaced with five copies of a 33-base pair ERE as described in Tzukerman et al., supra, was substituted for the MTV-LUC plasmid described herein. pRS-ß-Gal, coding for constitutive expression of E. coli ß-galactosidase (ß-Gal), was included as an internal control for evaluation of transfection efficiency and compound toxicity.

Six hours after transfection, media was removed and the cells were washed with phosphate-buffered saline (PBS). Media containing reference compounds (i.e. progesterone as a PR agonist, mifepristone ((11beta,17beta)-11-[4-(dimethylamino)phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one: RU486; Roussel Uclaf) as a PR antagonist;

dihydrotestosterone (DHT; Sigma Chemical) as an AR agonist and 2-OH-flutamide (the active metabolite of 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]pronanamide; Schering-Plough) as an AR antagonist; estradiol (Sigma) as an ER agonist and ICI 164,384 (N-butyl-3,17-dihydroxy-N-methyl-(7-alpha,17-beta)-estra-1,3,5(10)-triene-7-undecanamide; ICI Americas) as an ER antagonist; dexamethasone (Sigma) as a GR agonist and RU486 as a GR antagonist; and aldosterone (Sigma) as a MR agonist and spirolactone ((7-alpha-[acetylthio]-17-alpha-hydroxy-3-oxopregn-4-ene-21-carboxylic acid gamma-lactone; Sigma) as an MR antagonist) and/or the modulator compounds of the present invention in concentrations ranging from 10^{-12} to 10^{-5} M were added to the cells. Three to four replicates were used for each sample. Transfections and subsequivuent procedures were performed on a Biomek 1000 automated laboratory work station.

After 40 hours, the cells were washed with PBS, lysed with a Triton X-100-based buffer and assayed for LUC and ß-Gal activities using a luminometer or spectrophotometer, respectively. For each replicate, the normalized response (NR) was calculated as:

LUC response/ß-Gal rate

where ß-Gal rate = ß-Gal•1×10^{-5}/ß-Gal incubation time.

The mean and standard error of the mean (SEM) of the NR were calculated. Data was plotted as the response of the compound compared to the reference compounds over the range of the dose-response curve. For agonist experiments, the effective concentration that produced 50% of the maximum response (EC_{50}) was quantified. Agonist efficacy was a function (%) of LUC expression relative to the maximum LUC production by the reference agonist for PR, AR, ER, GR or MR. Antagonist activity was determined by testing the amount of LUC expression in the presence of a fixed amount of progesterone as a PR agonist, DHT as an AR agonist, estradiol as an ER agonist, dexamethasone as a GR agonist, or aldosterone as an MR agonist at the EC_{50} concentration. The concentration of test compound that inhibited 50% of LUC expression induced by the reference agonist was quantified (IC_{50}). In addition, the efficacy of antagonists was determined as a function (%) of maximal inhibition.

IR Binding assay

PR and GR Binding: In addition, the binding of the compounds of the present invention to the steroid receptors was also investigated according to the following methodology for PR and GR. PR and GR proteins were prepared from Baculovirus extracts by incorporating the appropriate cDNAs for human progesterone receptor A form (PR-A; P. Kastner et al., 9 *EMBO*, 1603 (1990), the disclosure of which is herein incorporated by reference) and human glucocorticoid receptor alpha (GRα) into appropriate baculovirus the expression plasmids as described in E.A. Allegretto et al., 268 *J. Biol. Chem.*, 26625 (1993); G. Srinivasan and B. Thompson, 4 *Mol. Endo.*, 209 (1990); and D.R. O'Reilly et al., In, "Baculovirus Expression Vectors", D.R. O'Reilly et al., eds., W.H. Freeman, New York, NY, pp. 139-179 (1992), the disclosures of which are herein incorporated by reference. Assay buffers consisted of the following: PR, 10% glycerol, 10 mM Tris, 1 mM EDTA, 12 mM monothioglycerol (MTG) and 1mM PMSF, pH = 7.5 @ 4^{o}C; GR, 10% glycerol, 25 mM sodium phosphate, 10 mM KF, 2mM DTT, 0.25 mM CHAPS, and 20 mM sodium molybdate, pH = 7.5.

The PR and GR steroid receptor binding assays were performed in the same manner. The final assay volume was 500 µL for PR and 250 µL for GR, and contained ~5 µg of extract protein for PR and ~50 mg for GR, as well as 2-4 nM of the appropriate [^{3}H] steroid (e.g, [^{3}H] progesterone and [^{3}H] dexamethasone, respectively) and varying concentrations of competing ligand at concentrations that ranged from 0 - 10^{-5} M. Incubations were carried out at 4^{o}C for 16 hours.

Non-specific binding was defined as that binding remaining in the presence of 500 nM of the appropriate unlabelled steroid. At the end of the incubation period, bound from free ligand were separated by either charcoal (PR) or hydroxylapatite (GR). The amount of bound tritiated hormone was determined by liquid scintillation counting of an aliquot (700 mL) of the supernatant fluid or the hydroxylapatite pellet.

AR Binding: For the whole cell binding assay, COS-1 cells in 96-well microtiter plates containing DMEM-10% FBS were transfected as described above with the following plasmid DNA: pRShAR (2 ng/well), pRS-ß-Gal (50 ng/well) and pGEM (48 ng/well). Six hours after transfection, media was removed, the cells were washed with PBS and fresh media was added. The next day, the media was changed to DMEM-serum free to remove any endogenous ligand that might be complexed with the receptor in the cells.

After 24 hours in serum-free media, either a saturation analysis to determine the K_d for tritiated dihydrotestosterone (^{3}H-DHT) on human AR or a competitive binding assay to evaluate the ability of test compounds to compete with ^{3}H-DHT for AR was performed. For the saturation analysis, media (DMEM-0.2% CA-FBS) containing ^{3}H-DHT (in concentrations ranging from 12 nM to 0.24 nM) in the absence (total binding) or presence (non-specific binding) of a 100-fold molar excess of unlabeled DHT were added to the cells. For the competitive binding assay, media containing 1 nM ^{3}H-DHT and test compounds in concentrations ranging from 10^{-10} to 10^{-6} M were added to the cells. Three replicates were used for each sample. After three hours at 37°C, an aliquot of the total binding media at each concentration of ^{3}H-DHT was removed to estimate the amount of free ^{3}H-DHT. The remaining media was removed, the cells were washed three times with PBS to remove unbound ligand, and cells were lysed with a Triton X-100-based buffer. The lysates were assayed for amount of bound ^{3}H-DHT and ß-Gal activity using a scintillation counter or spectrophotometer, respectively.

For the saturation analyses, the difference between the total binding and the nonspecific binding, normalized by the ß-Gal rate, was defined as specific binding. The specific binding was evaluated by Scatchard analysis to determine the K_d for ^{3}H-DHT. See e.g., D. Rodbard, "Mathematics and statistics of ligand assays: an illustrated guide" In: *J.* Langon and *J.J.* Clapp, eds., *Ligand Assay*, Masson Publishing U.S.A., Inc., New York, pp. 45-99, (1981), the disclosure of which is herein incorporated by reference. For the competition studies, the data was plotted as the amount of ^{3}H-DHT (% of control in the absence of test compound) remaining over the range of the dose-response curve for a given compound. The concentration of test compound that inhibited 50% of the amount of ^{3}H-DHT bound in the absence of competing ligand was quantified (IC_{50}) after log-logit transformation. The K_i values were determined by application of the Cheng-Prusoff equivuation to the IC_{50} values, where:

$$K_i = \frac{IC_{50}}{(1+[^3\text{H-DHT}])/K_d \text{ for } ^3\text{H-DHT}}$$

To date, binding assays have not been performed utilizing ER or MR proteins.

After correcting for non-specific binding, IC_{50} values were determined. The IC_{50} value is defined as the concentration of competing ligand needed to reduce specific binding by 50%. The IC_{50} value was determined graphically from a log-logit plot of the data. The K_i values were determined by application of the Cheng-Prusoff equivuation to the IC_{50} values, the labeled ligand concentration and the K_d of the labeled ligand.

The agonist, antagonist and binding activity assay results of selected steroid receptor modulator compounds of present invention and the standard reference compounds on PR, AR, ER, GR and MR, as well as the cross-reactivity of selected compounds on all of these receptors, are shown in Tables 1-5 below. Efficacy is reported as the percent maximal response observed for each compound relative to the reference agonist and antagonist compounds indicated above. Also reported in Tables 1-5 for each compound is its antagonist potency or IC_{50} (which is the concentration (nM), requivuired to reduce the maximal response by 50%), its agonist potency or EC_{50} (nM). PR, AR and GR protein binding activity (K_i in nM) is shown in Tables 1-2 and 4.

Table 1: Agonist, antagonist and binding activity of selected steroid receptor modulator compounds of present invention and the reference agonist compound, Progesterone (**Prog**), and reference antagonist compound, mifepristone (**RU486**), on PR.

Cmpd	**PR Agonist CV-1 Cells**		**PR Antagonist CV-1 Cells**		**PR Binding**
No.	**Efficacy (%)**	**Potency (nM)**	**Efficacy (%)**	**Potency (nM)**	**K_i (nM)**
103	na	na	91	780	372
104	39	2,750	71	120	82
109	na	na	87	138	23
116	nt	nt	85	549	38
117	na	na	68	462	na
124	74	1,600	36	10	4
126	124	2,400	58	145	11
132	22	6,400	76	80	31
150	24	3,200	91	24	17
152	na	na	82	130	53
161	47	203	75	209	3
163	77	15	45	3,617	1

Cmpd	PR Agonist CV-1 Cells		PR Antagonist CV-1 Cells		PR Binding
No.	Efficacy (%)	Potency (nM)	Efficacy (%)	Potency (nM)	K_i (nM)
191	26	9	74	150	1
195	89	13	na	na	3
210	72	16	na	na	3
220	147	33	na	na	1
221	105	117	na	na	4
228	114	40	na	na	3
271	na	na	78	32	10
286	na	na	84	155	61
291	na	na	79	46	4
310	na	na	70	260	7
313	26	300	94	140	87
328	86	2200	65	26	7
331	na	na	88	210	273
332	138	3	na	na	0.4
368	183	43	na	na	4
374	231	4	na	na	0.5
377	101	550	na	na	20
379	na	na	87	350	25
381	81	58	na	na	18
385	27	82	45	2300	31
389	133	17	na	na	4
391	na	na	65	120	187
400	na	na	68	370	14
401	43	600	na	na	150
452	119	2400	70	24	17
455	na	na	76	35	10
Prog	100	4	na	na	3
RU486	na	na	96	0.1	0.8

na = not active (i.e. efficacy of <20 and potency of >10,000)
nt = not tested

Table 2: Agonist, antagonist and binding activity of selected steroid receptor modulator compounds of present invention and the reference agonist compound, dihydrotestosterone (**DHT**), and reference antagonist compound, 2-hydroxyflutamide (**Flut**), on AR.

Cmpd	**AR Agonist CV-1 Cells**		**AR Antagonist CV-1 Cells**		**AR Binding**
No.	**Efficacy (%)**	**Potency (nM)**	**Efficacy (%)**	**Potency (nM)**	**K_i (nM)**
238$^{@}$	96	10	na	na	44
247	23	2,400	69	34	864
255	na	na	82	25	675
256	na	na	91	62	4,500
260	na	na	53	24	435
265	na	na	78	56	23
405	na	na	89	77	6
414	118	1	na	na	0.3
416	88	340	24	5009	388
417	na	na	74	21	23
418	na	na	63	200	1000
419	29	1800	74	46	60
420	40	2100	80	32	346
437	na	na	72	13	38
445	74	7	32	8450	13
DHT	100	6	na	na	2
Flut	na	na	87	26	2085

na = not active (i.e. efficacy of <20 and potency of >10,000)
$^{@}$ profiles as an AR antagonist *in vivo*

Table 3: Agonist, antagonist and binding activity of selected steroid receptor modulator compounds of present invention and the reference agonist compound, Estrogen (**Estr**), and reference antagonist compound, ICI 164,384 (**ICI 164**), on ER.

Cmpd	**ER Agonist CV-1 Cells**		**ER Antagonist CV-1 Cells**	
No.	**Efficacy (%)**	**Potency (nM)**	**Efficacy (%)**	**Potency (nM)**
161	nt	nt	86	505
170	nt	nt	78	580
191	nt	nt	93	330
192	na	na	80	195
194	nt	nt	94	390
195	90	1900	68	4406
Estr	100	7	na	na
ICI 164	na	na	99	43

na = not active (i.e. efficacy of <20 and potency of >10,000)
nt = not tested

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Table 4: Antagonist and binding activity of selected steroid receptor modulator compounds of present invention and the reference antagonist compounds, RU486 and Spironolactone (**Spir**), on GR and MR, respectively.

Cmpd	**GR Antagonist CV-1 Cells**		**MR Antagonist CV-1 Cells**		**GR Binding**
No.	**Efficacy (%)**	**Potency (nM)**	**Efficacy (%)**	**Potency (nM)**	**K_i (nM)**
161	97	600	58	1000	137
167	96	855	61	2000	21
170	94	1550	84	410	47
192	81	280	70	320	214
195	96	590	47	1900	26
RU486	100	1	77	1100	0.4
Spir	80	2000	96	25	nt

nt - not tested

Table 5: Overall agonist and antagonist potency of selected steroid receptor modulator compounds of present invention and the reference agonist and antagonist compounds shown in Tables 1-4 on PR, AR, ER, GR and MR.

Cmpd	**PR Potency**		**AR Potency**		**ER Potency**		**GR Potency**	**MR Potency**
No.	**Agon (nM)**	**Antag (nM)**	**Agon (nM)**	**Antag (nM)**	**Agon (nM)**	**Antag (nM)**	**Antag (nM)**	**Antag (nM)**
124	1600	10	nt	1500	2100	na	na	na
150	3200	24	nt	140	nt	na	2700	1900
163	15	3617	nt	1550	na	2150	1330	1450
170	73	145	nt	290	nt	580	1550	410
191	9	150	nt	520	nt	330	nt	nt
192	na	89	nt	79	nt	195	280	320
195	13	na	nt	470	1900	4406	590	1900
255	na	3050	na	25	na	na	na	na
260	na	230	na	24	nt	nt	nt	nt
Prog	4	na	1300	na	na	na	na	nt
RU486	na	0.1	na	12	na	1500	0.7	1100
DHT	na	1800	6	na	1700	na	na	nt
Flut	na	1900	na	26	na	na	na	na
Estr	nt	nt	na	na	7	na	na	nt

Cmpd	PR Potency		AR Potency		ER Potency		GR Potency	MR Potency
No.	Agon (nM)	Antag (nM)	Agon (nM)	Antag (nM)	Agon (nM)	Antag (nM)	Antag (nM)	Antag (nM)
ICI 164	na	na	na	na	na	160	na	na
Spir	nt	268	nt	nt	na	na	2000	25

na=not active (i.e., efficacy of >20 and potency of >10,000)
nt=not tested

As can be seen in the Tables, Compounds 163, 191, 332 and 374 are highly selective PR agonists, while Compounds 124, 150, 328 and 455 are highly selective PR antagonists. Importantly, these PR antagonist Compounds show very little or no cross reactivity on GR, or any of the other tested steroid receptors. In contrast, the known PR antagonist, RU486, shows strong cross reactivity on both GR and AR, showing essentially equivual potency as both a PR and GR antagonist. Thus RU486 may not be generally useful for long-term, chronic administration due to this undesirable GR cross reactivity. Furthermore, Compounds 255, 260, 417 and 437 of the present invention shown equivual or better activity as AR antagonists than the known antagonist compound 2-OH-flutamide.

EXAMPLE 359

The effectiveness of selected compounds of the present invention as PR agonists was investigated in the well recognized uterine wet weight assay, as described in G.J. Marcus, "Mitosis in the rat uterus during the estrous cycle, early pregnancy and early pseudopregnancy", 10 *Biol. Reprod.*, 447 (1974), S. Sakamoto et al., "Effects of estrogen and progesterone on thymidine kinase activity in the immature rat uterus", 145 *Am. J. Obstet. Gynecol.*, 711 (1983), and C.W. Emmens and R.I. Dorfman, "Estrogens" (Ch. 2) and "Antiestrogens" (Ch. 3). in *Methods in Hormone Research*, ed. R.I. Dorfman, Academic Press, New York, New York, pp101-130 (1969), the disclosures of which are herein incorporated by reference. Four to five week old, ovariectomized, Sprague-Dawely rats (Harlan-Sprague-Dawely, Indianapolis, IN) were obtained 1 week after surgery and allowed to acclimate for an additional week after shipment. Compound **163**, Compound **210**, medroxyprogesterone acetate (MPA) (Sigma, St. Louis, MO) a synthetic progesterone agonist, and estrone (E1) (Sigma, St. Louis, MO) a synthetic estrogen agonist, were fully dissolved in purified sesame oil (Croda, Parsippany, NJ). Animals were randomized into treatment groups (4 rats/group) and administered Compound **163**, Compound **210**, or MPA (0.3, 1.0 or 3.0 mg/rat, 0.5 mL volumes, oral, once a day for three days in the presence of estrone (10 µg/day, subcutaneous). Additional control groups of rats were administered estrone or vehicle (i.e. sesame oil) alone. Animals were sacrificed on the fourth day of the experiment. Upon necropsy, uterine wet weights were obtained, and are reported in Table 6 below.

Table 6: Mean uterine wet weights in presence of estrone (10 µg), MPA, a recognized PR agonist, and Compounds 163 and 210 of the present invention.

Group	E1 (µg)	MPA (mg)	Cmpd 163 (mg)	Cmpd 210 (mg)	Mean Uterine Wet Weight (mg)
Control	none	none	none	none	45
1	10	none	none	none	205
2	10	0.3	none	none	140
3	10	1.0	none	none	130
4	10	3.0	none	none	130
5	10	none	3.0	none	125
6	10	none	none	0.3	110
7	10	none	none	1.0	100
8	10	none	none	3.0	100

As can be seen in Table 6, estrone alone increased uterine wet weight 4-fold over control treated animals. MPA co-administered with estrone significantly decreased the uterine wet weight at doses of 0.3 mg, 1.0 mg, and 3.0 mg/rat. Compound **163** at a dosage of 3 mg/rat, decreased by approximately half, the mean uterine wet weight, as did Compound **210** at doses of 0.3 mg, 1.0 mg, and 3.0 mg/rat.

EXAMPLE 360

The activity of Compound 150 of the present invention as a PR antagonist was measured via an implantation assay, a recognized test of antiprogestin activity, as described in F.H.Bronson, et al., "Reproduction", In *Biology of the Laboratory Mouse*, 2nd ed., pp

187-204, McGraw Hill, New York, NY (1966), the disclosure of which is herein incorporated by reference. Virgin female mice (ICR strain) were caged with fertile males of the same strain overnight and examined the next morning for vaginal plugs (Day 1 of pregnancy). Mating was assumed to have taken place at 02.00 h, time 0.

The animals were treated orally with a known amount of the antiprogestin, mifepristone (RU486) or Compound 150 daily between days 2 and 4 of pregnancy. Compound 150 was dissolved in sesame oil (50 mg/mL) and kept at room temperature before use. RU486 was first dissolved in 100% ethanol and diluted to a concentration of 10 mg/mL with sesame oil. Control animals received an equivuivalent volume of the control vehicle, sesame oil, alone.

The animals were sacrificed, and autopsies were carried out at Day 8 of pregnancy, and numbers of implantation sites counted and recorded, and are shown in Table 7 below. Each group consisted of between 5 and 7 animals.

Table 7: Percent pregnancy rate in mice in the presence of RU486 (mifepristone) a recognized PR antagonist, and Compound 150 of the present invention.

Group	**RU486 (mg/day)**	**Cmpd 150 (mg/day)**	**Percent Pregnancy Rate**
Control	none	none	100
1	1.0	none	0
2	none	2.5	50
3	none	5.0	0

As can be seen from Table 7, the control group of mice exhibited a pregnancy rate of one hundred. Administration of 1.0 mg/day of RU486 resulted in a pregnancy rate of zero, while administration of Compound 150 at 2.5 mg/day and 5.0 mg/day resulted in pregnancy rates of 50 and 0, respectively. In addition, the above noted effect on pregnancy rate of Compound 150 was reversed to the control level by the simultaneous injection of the known PR agonist Compound R5020 (promegestone; (17β)-17-methyl-17-(1-oxopropyl) estra-4,9-dien-3-one; New England Nuclear, Boston, MA) at a dose of 1.0 mg per day.

EXAMPLE 361

The activity of selected compounds of the present invention as AR antagonists was investigated in an immature castrated male rat model, a recognized test of the antiandrogen activity of a given compound, as described in L.G. Hershberger et al., 83 *Proc. Soc. Exptl. Biol. Med.*, 175 (1953); P.C. Walsh and R.F. Gittes, "Inhibition of extratesticular stimuli to prostatic growth in the castrated rat by antiandrogens", 86 *Endocrinology*, 624 (1970); and B.J. Furr et al., "ICI 176,334: A novel non-steroidal, peripherally selective antiandrogen", 113 *J. Endocrinol.*, R7-9 (1987), the disclosures of which are herein incorporated by reference.

The basis of this assay is the fact that the male sexual accessory organs, such as the prostate and seminal vesicles, play an important role in reproductive function. These glands are stimulated to grow and are maintained in size and secretory function by the continued presence of serum testosterone (T), which is the major serum androgen (>95%) produced by the Leydig cells in the testis under the control of the pituitary luteinizing hormone (LH) and follicle stimulating hormone (FSH). Testosterone is converted to the more active form, dihydrotestosterone (DHT), within the prostate by 5α-reductase. Adrenal androgens also contribute about 20% of total DHT in the rat prostate, and about 40% of that in 65-year-old men. F. Labrie et al.. 16 *Clin. Invest. Med.*, 475-492 (1993). However, this is not a major pathway, since in both animals and humans, castration leads to almost complete involution of the prostate and seminal vesicles without concomitant adrenalectomy. Therefore, under normal conditions, the adrenals do not support significant growth of prostatic tissue. M.C. Luke and D.S. Coffey, "The Physiology of Reproduction" ed. by E. Knobil and J.D. Neill, *1*, 1435-1487 (1994). Since the male sex organs are the tissues most responsive to modulation of androgen activity, this model is used to determine the androgen-dependent growth of the sex accessory organs in immature castrated rats.

Male immature rats (60-70 g, 23-25-day-old, Sprague-Dawley, Harlan) were castrated under metofane anesthesia. Five days after surgery, animals groups were dosed for 3 days as follows:

(1) control vehicle
(2) Testosterone Propionate (TP)(0.1 mg/rat/day, sub cutaneous)
(3) TP plus flutamide, a recognized antiandrogen, as a reference

compound, and/or a compound of the present invention (different doses, oral administration, daily) to demonstrate antagonist activity, or

(4) a compound of the present invention alone (different doses, oral administration daily) to demonstrate agonist activity

At the end of the 3-day treatment, the animals were sacrificed, and the ventral prostates (VP) and seminal vesicles (SV) were collected and weighed. To compare data from different experiments, the sexual organ weights were first standardized as mg per 100 g of body weight, and the increase in organ weight induced by TP was considered as the maximum increase (100%). Super-anova (one factor) was used for statistical analysis.

The gain and loss of sexual organ weights reflect the changes of cell number (DNA content) and cell mass (protein content), depending upon the serum androgen concentration. See Y. Okuda et al., 145 *J Urol.*, 188-191 (1991), the disclosure of which is herein incorporated by reference.. Therefore, measurement of organ wet weights is sufficient to indicate the bioactivity of androgens and androgen antagonists. In immature castrated rats, replacement of exogenous androgens increased the weights of the ventral prostate (VP) and the seminal vesicles (SV) in a dose-dependent manner as shown in Table 8.

Table 8: TP-Induced Ventral Prostate and Seminal Vesicle Growth in castrated immature rats, with oral dosing once daily, for 3 days.

Treatment (mg TP)	**VP (wet wt)**	**%VP growth**	**SV (wet wt)**	**%SV growth**
0	10.5±1.0	100	7.5±0.6	100
0.01	15.4±0.6	146.5	12.3±0.8	165.1
0.03	23.5±1.3	224.1	27.5±0.8	369.5
0.1	35.3±2.1	337.0	42.0±2.0	563.8
0.3	43.6±1.1	415.9	45.9±1.9	616.1
1	44.8±3.7	427.4	51.0±5.4	684.6

The maximum increase in organ wet weights was 4 to 5-fold when dosing 3 mg/rat/day of testosterone (T) or 1 mg/rat/day of testosterone propionate (TP) for 3 days.

The EC_{50} of T and TP were about 1 mg and 0.03 mg, respectively. The increase in the weights of VP and SV also correlated with the increase in the serum T and DHT concentrations. Although administration of T showed 5-times higher serum concentrations of T and DHT at 2 hours after subcutaneous injection than that of TP, thereafter, these high levels declined very rapidly. In contrast, the serum concentrations of T and DHT in TP-treated animals were fairly consistent during the 24 hours, and therefore, TP showed about 10-30-fold higher potency than free T.

In this immature castrated rat model, a known AR antagonist (flutamide) was also administered simultaneously with 0.1 mg of TP (ED_{80}), inhibiting the testosterone-mediated increases in the weights of VP and SV in a dose-dependent manner as shown in Table 9. The antagonist effects were similar when dosing orally or subcutaneously. Compounds 255 and 261 also exhibited AR antagonist activity by suppressing the testosterone-mediated increases in the weights of the VP and SV, as summarized in Table 9.

Table 9: Inhibition of TP-InducedVentral Prostate and Seminal Vesicle Growth in castrated immature rats at oral dosing, once daily, for 3 days of flutamide (flut), Compound 255 or Compound 261.

Treatment	VP (wet wt)	VP wt (% of TP (0.1) control)	SV (wet wt)	SV wt (% of TP (0.1) control)
Control	9.8±1.2	36.2	9.9±0.9	21.7
TP (0.1)	25.5±1.2	100	33.6±4.0	100
TP+ flut (1.0)	12.4±1.1	49.9	8.5±0.6	30.3
TP+ flut (3.0)	9.5 ±0.4	37.4	9.8±0.5	29.3
TP+ 255 (0.3)	22.1±0.7	86.4	29.8±2.5	88.7
TP+ 255 (1.0)	20.0±4.5	78.2	24.8±9.0	73.9
TP+ 255 (3.0)	17.3±1.2	67.7	20.4±1.2	60.6
TP+ 261 (1.0)	21.0±1.7	84.4	23.8±1.8	85.0
TP+ 261 (3.0)	16.7±1.0	67.1	20.8±1.3	74.2

Pharmacological and Other Applications

As will be discernible to those skilled in the art, the non-steroid modulator compounds of the present invention can be readily utilized in pharmacological applications where PR, AR, ER, GR and/or MR antagonist or agonist activity is desired, and where it is desired to minimize cross reactivities with other steroid receptor related IRs. In vivo applications of the invention include administration of the disclosed compounds to mammalian subjects, and in particular to humans.

The following Example provides illustrative pharmaceutical composition formulations:

EXAMPLE 362

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
COMPOUND 191	140
Starch, dried	100
Magnesium stearate	10
Total	250 mg

The above ingredients are mixed and filled into hard gelatin capsules in 250 mg quantities.

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
COMPOUND 191	140
Cellulose, microcrystalline	200
Silicon dioxide, fumed	10
Stearic acid	10
Total	360 mg

The components are blended and compressed to form tablets each weighing 665 mg.

Tablets, each containing 60 mg of active ingredient, are made as follows:

	Quantity (mg/tablet)
COMPOUND 191	60
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (PVP) (as 10% solution in water)	4
Sodium carboxymethyl starch (SCMS)	4.5
Magnesium stearate	0.5
Talc	1.0
Total	150 mg

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of PVP is mixed with the resultant powders, which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50° C and passed through a No. 18 mesh U.S. sieve. The SCMS, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, and then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Suppositories, each containing 225 mg of active ingredient, may be made as follows:

COMPOUND 191	225 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,225 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of normal 2g capacity and allowed to cool.

An intravenous formulation may be prepared as follows:

COMPOUND 191	100 mg
Isotonic saline	1,000 mL
Glycerol	100 mL

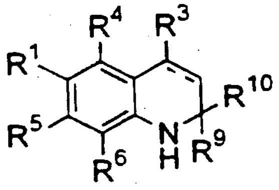
The compound is dissolved in the glycerol and then the solution is slowly diluted with isotonic saline. The solution of the above ingredients is then administered intravenously at a rate of 1 mL per minute to a patient.

While in accordance with the patent statutes, description of the preferred embodiments and processing conditions have been provided, the scope of the invention is not to be limited thereto or thereby. Various modifications and alterations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention.

Consequently, for an understanding of the scope of the present invention, reference is made to the following claims.

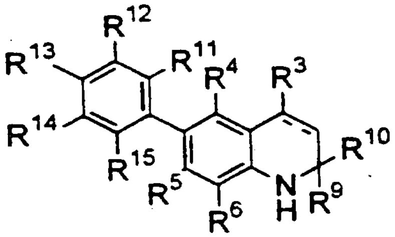
What is claimed is:

1. A compound having the formulae:



(I)

OR



(II)

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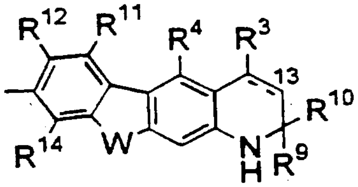

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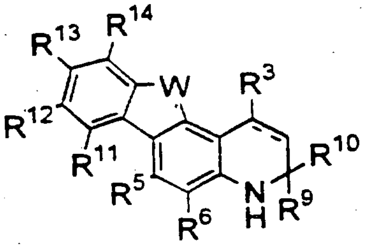

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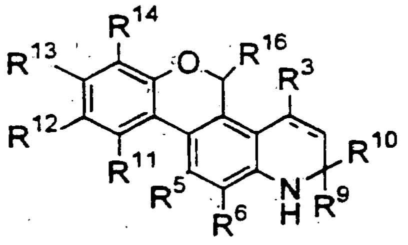

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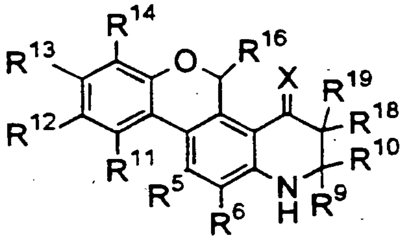

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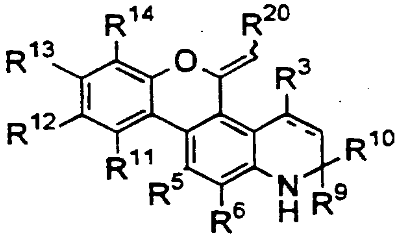

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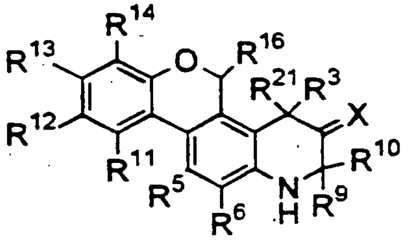

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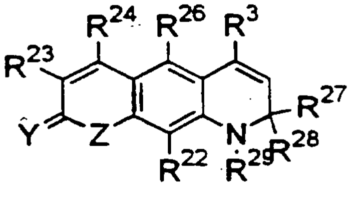

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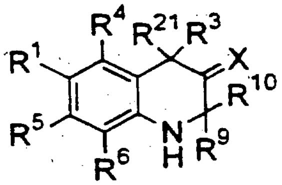

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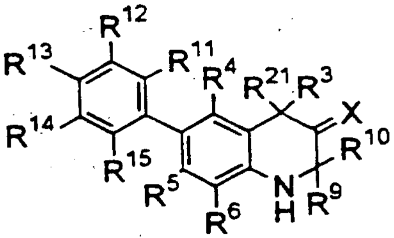

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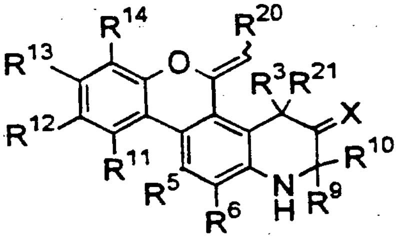

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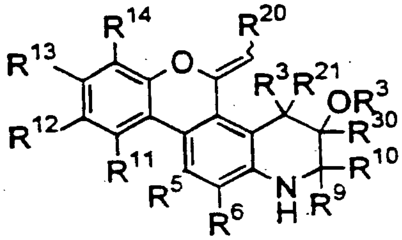

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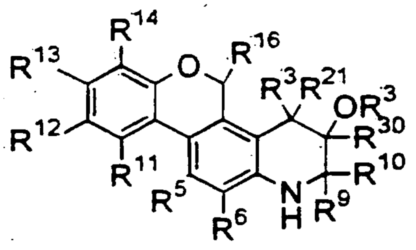

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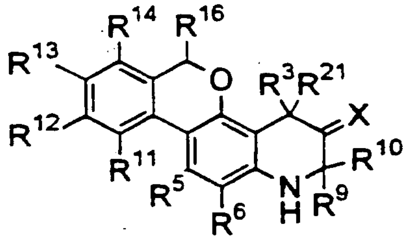

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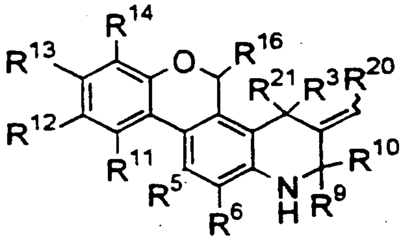

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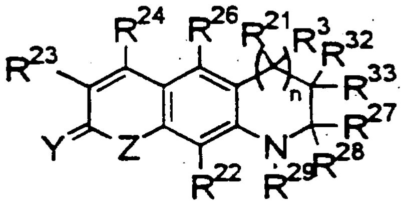

(XVII)

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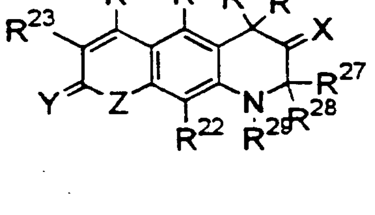

(XVIII)

wherein:

R^1 is a heteroaryl optionally substituted with a C_1 - C_4 alkyl, F, Cl, Br, NO_2, CO_2H, CO_2R^2, CHO, CN, CF_3, CH_2OH or $COCH_3$, where R^2 is hydrogen, a C_1 - C_4 alkyl or perfluoroalkyl, aryl, heteroaryl or optionally substituted allyl, arylmethyl, alkynyl or alkenyl, and where said R^1 heteroaryl is attached to compounds of formulas I and X through a carbon or nitrogen atom;

R^3 is hydrogen, a C_1 - C_4 alkyl or perfluoroalkyl, hydroxymethyl, aryl, heteroaryl or optionally substituted allyl, arylmethyl, alkynyl or alkenyl;

R^4 through R^6 each independently are hydrogen, F, Cl, Br, I, NO_2, CO_2H, CO_2R^2, COR^2, CN, CF_3, CH_2OH, a C_1-C_4 alkyl or perfluoroalkyl, OR^2, SR^2, $S(O)R^2$, SO_2R^2, SO_3H, $S(NR^2R^7)R^2$, $S(O)(NR^2R^7)R^2$, NR^2R^7, aryl, heteroaryl or optionally substituted allyl, arylmethyl, alkynyl or alkenyl, where R^2 has the definition given above, R^7 is hydrogen, a C_1 - C_4 alkyl or perfluoroalkyl, aryl, heteroaryl, optionally substituted allyl or arylmethyl, OR^8 or NHR^8, where R^8 is hydrogen, a C_1 - C_6 alkyl or perfluoroalkyl, aryl, heteroaryl, optionally substituted allyl or arylmethyl, SO_2R^2 or $S(O)R^2$;

R^9 and R^{10} each independently are hydrogen, a C_1 - C_6 alkyl or perfluoroalkyl, aryl, heteroaryl or optionally substituted allyl, arylmethyl, alkynyl or alkenyl, or R^9 and R^{10} taken together can form a three- to seven-membered ring optionally substituted with hydrogen, F, OR^2, or NR^2R^7, where R^2 and R^7 have the definitions given above;

R^{11} through R^{15} each independently are hydrogen, F, Cl, Br, I, NO_2, CO_2H, CO_2R^2, COR^2, CN, CF_3, CH_2OH, a C_1-C_4 alkyl or perfluoroalkyl, OR^2, SR^2, $S(O)R^2$, SO_2R^2, SO_3H, $S(NR^2R^7)R^2$, $S(O)(NR^2R^7)R^2$, NR^2R^7, aryl, heteroaryl or optionally substituted allyl, arylmethyl, alkynyl or alkenyl, where R^2, R^7 and R^8 have the definitions given above;

W is O, NH, NR^7, CH_2, CHOH, C=O, OC=O, O=CO, NR^7C=O, NHC=O, O=CNR^7, O=CNH, SC=O, O=CS, or $CHOCOR^7$, where R^7 has the definition given above, except that when W is NH, CH_2 or O in the compounds of formula III, then R^{11} through R^{14} and R^4 cannot all be hydrogen when R^3, R^9 and R^{10} are all CH_3, nor can they be a single F, Cl or Br substituent with the remaining substituents all being hydrogen when R^3, R^9 and R^{10} are all CH_3, and further except that when W is O or NH in the compounds of formula IV, then R^5 through R^6 and R^{11} through R^{14} cannot all be hydrogen when R^3, R^9 and R^{10} are all CH_3;

X is CH_2, O, S or NR^7, where R^7 has the definition given above;

R^{16} is hydrogen, OH, OR^{17}, SR^{17}, NR^2R^7, optionally substituted allyl, arylmethyl, alkynyl, alkenyl, aryl, heteroaryl or C_1 - C_{10} alkyl, where R^{17} is a C_1 - C_{10} alkyl or perfluoroalkyl, or is an optionally substituted allyl, arylmethyl, aryl or heteroaryl, and where R^2 and R^7 have the definitions given above;

R^{18} and R^{19} each independently are hydrogen, a C_1 - C_6 alkyl or perfluoroalkyl, aryl, heteroaryl or optionally substituted allyl, arylmethyl, alkynyl or alkenyl, or R^{18} and R^{19} taken together can form a three- to seven-membered ring optionally substituted with hydrogen, F, OR^2, or NR^7R^8, where R^2, R^7 and R^8 have the definitions given above;

R^{20} is a C_1 - C_6 alkyl or an optionally substituted allyl, arylmethyl, alkenyl, aryl or heteroaryl;

R^{21} is hydrogen, a C_1 - C_4 alkyl or optionally substituted allyl, arylmethyl, aryl or heteroaryl;

R^{22} is hydrogen, a C_1 - C_4 alkyl, F, Cl, Br, I, OR^2, NR^2R^7 or SR^2, where R^2 and R^7 have the definitions given above;

R^{23} is hydrogen, Cl, Br, OR^8, NR^2R^7, a C_1 - C_4 alkyl or perhaloalkyl, or is an optionally substituted allyl, arylmethyl, alkynyl, alkenyl, aryl or heteroaryl, where R^2, R^7 and R^8 have the definitions given above;

R^{24} is hydrogen, F, Br, Cl, a C_1 - C_4 alkyl or perhaloalkyl, aryl, heteroaryl, CF_3, CF_2OR^{25}, CH_2OR^{25}, or OR^{25}, where R^{25} is a C_1 - C_4 alkyl, except that R^{24} cannot be CH_3 when Z is O, R^{22}, R^{23}, R^{26} and R^{29} are all hydrogen and R^3, R^{27} and R^{28} all are CH_3;

R^{26} is hydrogen, a C_1 - C_4 alkyl, F, Cl, Br, I, OR^2, NR^2R^7 or SR^2, where R^2 and R^7 have the definitions given above;

R^{27} and R^{28} each independently are hydrogen, a C_1 - C_4 alkyl or perfluoroalkyl, heteroaryl, optionally substituted allyl, arylmethyl, alkynyl or alkenyl, or an aryl optionally substituted with hydrogen, F, Cl, Br, OR^2 or NR^2R^7, or R^{27} and R^{28} taken together can form a three- to seven-membered ring optionally substituted with hydrogen, F, Cl, Br, OR^2 or NR^2R^7, where R^2 and R^7 have the definitions given above;

R^{29} is hydrogen, a C_1 - C_6 alkyl or an optionally substituted allyl, arylmethyl, aryl or heteroaryl;

R^{30} and R^{31} each independently are hydrogen, a C_1 - C_6 alkyl or an optionally substituted allyl, arylmethyl, aryl or heteroaryl, or R^{30} and R^{31} taken together can form a three- to seven-membered ring optionally substituted with hydrogen, F, Cl, OR^2 or NR^2R^7, where R^2 and R^7 have the definitions given above;

R^{32} and R^{33} each independently are hydrogen, a C_1 - C_4 alkyl or an aryl optionally substituted with hydrogen, F, Cl, Br, OR^2 or NR^2R^7, or R^{32} and R^{33} taken together can form a three- to seven-membered ring optionally substituted with hydrogen, F, Cl, Br, OR^2 or NR^2R^7, where R^2 and R^7 have the definitions given above;

n is 0 or 1;

Y is O or S;

Z is O, S, NH, NR^2 or $NCOR^2$, where R^2 has the same definition given above;

the wavy line in the compounds of formulas VII, XII, XIII and XVI represent an olefin bond in either the *cis* or *trans* configuration; and

the dotted lines in the structures depict optional double bonds, except that when there is a C_3 - C_4 double bond in the nitrogen bearing ring of compounds of formula II, then R^{11} through R^{15} cannot all be hydrogen and R^3, R^9 and R^{10} cannot all be methyl, and further except when R^{23} is an aryl, R^{22}, R^{24} and R^{29} are all hydrogen, R^3 is CH_3 and Z is NR^2, then R^2 cannot be a C_1 - C_4 alkyl.

2. A compound according to claim 1, wherein the compounds of formulae I through XVIII comprise steroid receptor modulator compounds.

3. A compound according to claim 2, wherein the compounds of formulae I, II, III, IV, X and XI comprise PR antagonists.

4. A compound according to claim 2, wherein the compounds of formulae V and VI comprise PR modulators.

5. A compound according to claim 2, wherein the compounds of formulae VII, VIII, XII, XIII, XIV, XV and XVI comprise PR agonists.

6. A compound according to claim 2, wherein the compounds of formulae IX, XVII and XVIII comprise AR modulators.

7. A compound according to claim 6, wherein the compounds of formulae IX and XVII comprise AR antagonists.

8. A PR antagonist compound according to claim 3 selected from the group consisting of 1,2,3,4-Tetrahydro-2,2,4-trimethyl-6-phenylquinoline (Compound 100); 1,2-Dihydro-2,2,4-trimethyl-6-(1,2,3-thiadiazol-5-yl)quinoline (Compound 101); 1,2-Dihydro-2,2,4-trimethyl-6-(1,3-oxazol-5-yl)quinoline (Compound 102); 6-(4,5-Dichloroimidazol-1-yl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 103); 6-(4-Bromo-1-methylpyrazol-3-yl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 104); 1,2-Dihydro-2,2,4-trimethyl-6-(3-pyridyl)quinoline (Compound 105); 6-(4-Fluorophenyl)-1,2,-dihydro-2,2,4-trimethylquinoline (Compound 106); 1,2-Dihydro-6-(3-trifluoromethylphenyl)-2,2,4-trimethylquinoline (Compound 107); 1,2-Dihydro-2,2,4-trimethyl-6-(4-nitrophenyl)quinoline (Compound 108); 6-(2,3-Dichlorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 109); 1,2-Dihydro-6-(2-hydroxycarbonyl-4-nitrophenyl)-2,2,4-trimethylquinoline (Compound 110); 6-(3,4-Dichlorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 111); 4-Ethyl-1,2-dihydro-2,2-dimethyl-6-phenylquinoline (Compound 112); 1,2-Dihydro-2,2-dimethyl-6-phenyl-4-propylquinoline (Compound 113); 6-(2-Chlorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 114); 1,2-Dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound 115); 1,2-Dihydro-2,2,4-trimethylindeno[2,1-*f*]quinoline (Compound 116); 8-Bromo-1,2-dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound 117); 1,2-Dihydro-2,2,4-trimethylbenzo[b]furano[3,2,*g*]quinoline (Compound 118); 1,2-Dihydro-2,2,4-trimethylbenzo[b]furano[2,3-*f*]quinoline (Compound 119); 6-Fluoro-1,2-dihydro-2,2,4-trimethylindeno[2,1-*f*]quinoline (Compound 120); 9-Fluoro-1,2-dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound 121); 1,2-Dihydro-9-hydroxylmethyl-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound 122); 8-Chloro-1,2-dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound 123); 8-Fluoro-1,2-dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound 124); 8-Acetyl-1,2-dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound 125); 6-Fluoro-1,2-dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound 126); 7-Bromo-1,2-dihydro-2,2,4-trimethylindeno[2,1-*f*]quinoline (Compound 127); 1,2-Dihydro-2,2,4-trimethyl-7-nitroindeno[2,1-*f*]quinoline (Compound 128); 1,2-Dihydro-2,2,4-trimethyl-8-

nitroindeno[1,2-*g*]quinoline (Compound 129); 6,9-Difluoro-1,2-dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound 130); 7-Fluoro-1,2-dihydro-2,2,4-trimethyl-11-(thiomethyl)indeno[2,1-*f*]quinoline (Compound 131); 5,8-Difluoro-1,2-dihydro-10-hydroxy-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound 132); 7,9-Difluoro-1,2-dihydro-10-hydroxy-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound 133); 7,10-Difluoro-1,2-dihydro-2,2,4-trimethyl-5-oxoindeno[3,2-*f*]quinoline (Compound 134); 7,9-Difluoro-1,2-dihydro-2,2,4-trimethyl-10-oxoindeno[1,2-*g*]quinoline (Compound 135); 8-Fluoro-1,2-dihydro-10-hydroxy-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound 136); 8-Fluoro-1,2-dihydro-2,2,4-trimethyl-10-oxoindeno[1,2-*g*]quinoline (Compound 137); 7-Fluoro-1,2-dihydro-2,2,4-trimethyl-8-nitroindeno[1,2-*g*]quinoline (Compound 138); 5-Chloro-1,2-dihydro-10-hydroxy-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound 139); 6-Fluoro-1,2-dihydro-2,2,4-trimethyl-10-oxoindeno[1,2-*g*]quinoline (Compound 140); 6-Fluoro-1,2-dihydro-10-hydroxy-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound 141); 5,8-Difluoro-1,2-dihydro-2,2,4-trimethyl-10-(trifluoroacetoxy)indeno[1,2-*g*]quinoline (Compound 142); 6-(3,5-Difluorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (Compound 143); 1,2-Dihydro-2,2,4-trimethylindolo[3,2-*g*]quinoline (Compound 144); 5-Ethyl-1,2-dihydro-2,2,4-trimethylindolo[2,3-*f*]quinoline (Compound 145); 6-(3-Chlorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 146); 6-(3,5-Difluorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 147); 6-(3-Fluorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 148); 1,2-Dihydro-2,2,4-trimethyl-6-(4-pyridyl)quinoline (Compound 149); 6-(3-Cyanophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 150); 6-(3,5-Dichlorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 151); 6-(2,3-Difluorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 152); 1,2-Dihydro-2,2,4-trimethyl-6-(pentafluorophenyl)quinoline (Compound 153); 1,2-Dihydro-2,2,4-trimethyl-6-[4-(trifluoroacetyl)phenyl]quinoline (Compound 154); 1,2-Dihydro-2,2,4-trimethyl-6-(1,3-pyrimid-5-yl)quinoline (Compound 155); 6-(3-Cyanophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (Compound 156); 5,8-Difluoro-1,2-dihydro-2,2,4-trimethylindeno[1,2-*g*]quinoline (Compound 157); 7,10-Difluoro-1,2-dihydro-2,2,4-trimethylindeno[2,1-*f*]quinoline (Compound 158); 8-Cyano-1,2-dihydro-2,2,4-trimethylindeno[3,2-*e*]quinoline (Compound 270); 6-(3-Cyano-5-fluorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline

(Compound 271); 6-(3-Cyano-4-fluorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 272); 6-(3-Cyano-6-fluorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 273); 6-[5-fluoro-3-(trifluoromethyl)phenyl]-1,2-dihydro-2,2,4-trimethylquinoline (Compound 274); 6-(3-chloro-2-methylphenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 275); 1,2-Dihydro-2,2,4-trimethyl-6-(3-nitrophenyl)quinoline (Compound 276); 6-(3-Acetylphenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 277); 6-(3-cyano-2-methylphenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 278); 1,2-Dihydro-2,2,4-trimethyl-6-(3-methylphenyl)quinoline (Compound 279); 6-(5-Fluoro-3-nitrophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 280); 1,2-Dihydro-6-(3-methoxyphenyl)-2,2,4-trimethylquinoline (Compound 281); 6-(5-Cyano-3-pyridyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 282); 1,2-Dihydro-2,2,4-trimethyl-6-(2-methyl-3-nitrophenyl)quinoline (Compound 283); 6-(2-Amino-3,5-difluorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 284); 6-(3-Bromo-2-chloro-5-fluorophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 285); 6-(3-Cyano-5-fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-3-quinolone (Compound 286); 6-(3-Fluoro-2-methylphenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 287); 1,2-Dihydro-2,2,4-trimethyl-6-(3-methylthiophenyl)quinoline (Compound 288); 6-(5-Chloro-2-thienyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 289); 1,2-Dihydro-2,2,4-trimethyl-6-(3-methyl-2-thienyl)quinoline (Compound 290); 8-Fluoro-1,2-dihydro-2,2,4-trimethyl-6-(3-nitrophenyl)quinoline (Compound 291); 1,2-Dihydro-6-(3-nitrophenyl)-2,2,4,8-tetramethylquinoline (Compound 292); 6-(5-Bromo-3-pyridyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 293); 6-(3-Bromo-2-pyridyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 294); 6-(3-Bromo-2-thienyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 295); 1,2-Dihydro-6-(2,3,5,6-tetrafluoro-4-pyridyl)-2,2,4-trimethylquinoline (Compound 296); 5,8-Difluoro-1,2-dihydro-6-(3-nitrophenyl)-2,2,4-trimethylquinoline (Compound 297); 2,4-Diethyl-8-fluoro-1,2-dihydro-2-methyl-6-(3-nitrophenyl)quinoline (Compound 298); 6-(3-Bromophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 299); 1,2-Dihydro-2,2,4-trimethyl-6-(5-nitro-2-thienyl)quinoline (Compound 300); 1,2-Dihydro-6-(2,4,5-trifluorophenyl)-2,2,4-trimethylquinoline (Compound 301); 6-(3-Bromo-5-fluorophenyl)-1,2-dihydro-2,2,4-

trimethylquinoline (Compound 302); 6-(5-Carboxaldehyde-3-thienyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 303); 1,2-Dihydro-2,2,4,7-tetramethyl-6-(3-nitrophenyl)quinoline (Compound 304); 6-(5-Fluoro-2-methoxy-3-nitrophenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 305); 6-(3-Chloro-2-methoxyphenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 306); 1,2-Dihydro-2,2,4-trimethyl-6-(2,3,4-trifluorophenyl)quinoline (Compound 307); 6-(3-Bromo-2-methylphenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 308); 7-Chloro-1,2-dihydro-2,2,4-trimethyl-6-(3-nitrophenyl)quinoline (Compound 309); 5-Chloro-1,2-dihydro-2,2,4-trimethyl-6-(3-nitrophenyl)quinoline (Compound 310); 8-Chloro-1,2-dihydro-2,2,4-trimethyl-6-(3-nitrophenyl)quinoline (Compound 311); 8-Ethyl-1,2-dihydro-2,2,4-trimethyl-6-(3-nitrophenyl)quinoline (Compound 312); 9-Chloro-1,2-dihydro-2,2-dimethyl-5-coumarino[3,4-*f*]quinoline (Compound 313); 1,2-Dihydro-9-methoxy-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound 314); 9-Fluoro-1,2-dihydro-2,2,4,11-tetramethyl-5-coumarino[3,4-*f*]quinoline (Compound 315); 1,2-Dihydro-2,2,4,9-tetramethyl-5-coumarino[3,4-*f*]quinoline (Compound 316); 7-Chloro-1,2-dihydro-2,2,4-trimethyl-5-coumarino[3,4-*f*]quinoline (Compound 317); (*R/S*)-9-Chloro-1,2-dihydro-5-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 319); (*R/S*)-9-Fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 328); 6-(5-Cyano-2-thienyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 451); 6-(5-Cyano-3-thienyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 452); 6-(3-Formylphenyl)-1,2-dihydro-2,2,4-trimethylquinoline (Compound 453); 1,2-Dihydro-2,2,4-trimethyl-6-[3-(methylsulfonyl)phenyl]quinoline (Compound 454); (*R/S*)-6-(3-Cyano-5-fluorophenyl)-1,2,3,4-Tetrahydro-2,2,4-trimethylquinoline (Compound 455); and (*R/S*)-9-Chloro-1,2-dihydro-2,2,4-trimethyl-5-phenyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 456).

9. A PR modulator compound according to claim 4 selected from the group consisting of (*R/S*)-5-Butyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 160); (*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-phenyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 161); (*R/S*)-1,2,3,4-Tetrahydro-2,2-dimethyl-4-methylidene-5-phenyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 162); (*R/S*)-5-(4-Chlorophenyl)-1,2-dihydro-2,2,4-

trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 163); (*R/S*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylidene-*5H*-chromeno[3,4-*f*]quinoline (Compound 164); (*R/S*)-5-(4-Fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 165); (*R/S*)-5-(4-Acetylphenyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 166); (*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-(4-methylphenyl)-*5H*-chromeno[3,4-*f*]quinoline (Compound 167); (*R/S*)-1,2-Dihydro-5-(4-methoxyphenyl)-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 168); (*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-[4-(trifluoromethyl)phenyl]-*5H*-chromeno[3,4-*f*]quinoline (Compound 169); (*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-(thiophen-3-yl)-*5H*-chromeno[3,4-*f*]quinoline (Compound 170); (-)-1,2-Dihydro-2,2,4-trimethyl-5-(4-methylphenyl)-*5H*-chromeno[3,4-*f*]quinoline (Compound 171); (-)-5-(4-Chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 172); (*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-(3-methylphenyl)-*5H*-chromeno[3,4-*f*]quinoline (Compound 173); (+)-(4*l*,5*l*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 174); (-)-(4*l*,5*l*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 175); (*R/S*-4*l*,5*u*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 176); (*R/S*)-5-(3-Chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 177); (*R/S*)-5-(3-Chlorophenyl)-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylidene-*5H*-chromeno[3,4-*f*]quinoline (Compound 178); (*R/S*)-5-(4-Bromophenyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 179); (*R/S*)-5-(4-Bromophenyl)-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylidene-*5H*-chromeno[3,4-*f*]quinoline (Compound 180); (*R/S*)-5-(3-Bromophenyl)-1, 2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 181); (*R/S*)-5-(3-Bromophenyl)-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylidene-*5H*-chromeno[3,4-*f*]quinoline (Compound 182); (*R/S*)-5-(3,4-Dichlorophenyl)-1, 2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 183); (*R/S*)-5-(3-Bromo-2-pyridyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 184); (*R/S*)-1,2-Dihydro-5-hydroxy-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 185); (*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-methoxy-*5H*-chromeno[3,4-*f*]quinoline (Compound 186); (*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-propoxy-*5H*-chromeno[3,4-*f*]quinoline (Compound 187); (*R/S*)-5-Allyl-

1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 188); (*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-propyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 189); (*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-(2-pyridyl)-*5H*-chromeno[3,4-*f*]quinoline (Compound 190); (*R/S*)-5-(3-Fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 191); (*R/S*)-5-(3-Fluorophenyl)-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylidene-5H-chromeno[3,4-*f*]quinoline (Compound 192); (*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-propylthio-*5H*-chromeno[3,4-*f*]quinoline (Compound 193); (*R/S*)-1,2-Dihydro-5-(3-methoxyphenyl)-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 194); (*R/S*) 1,2-Dihydro-2,2,4-trimethyl-5-[3-(trifluoromethyl)phenyl]-*5H*-chromeno[3,4-*f*]quinoline (Compound 195); (*R/S*)-5-(3-Fluoro-4-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 196); (*R/S*)-5-(4-Bromo-3-pyridyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 197); (*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-(3-pyridyl)-*5H*-chromeno[3,4-*f*]quinoline (Compound 198); (*R/S*)-5-(4-Chloro-3-fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 199); (*R/S*)-1,2-Dihydro-2,2,4,5-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 200); (*R/S*)-1,2-Dihydro-5-hexyl-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 201); 1,2-Dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 202); (*R/S*)-1,2-Dihydro-5-(3-methylbutyl)-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 203); (*R/S*)-5-(4-Chlorobutyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 204); (*R/S*)-5-Benzyl-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 205); (*R/S*)-5-(4-Bromobutyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 206); (*R/S*)-5-Butyl-9-fluoro-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 210); (*R/S*)-5-Butyl-8-fluoro-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 211); (*R/S*)-5-(3-Chlorophenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 212); (*R/S*)-5-(4-Chloro-3-methylphenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 213); (*R/S*)-5-(4-Chlorophenyl)-9-fluoro-1,2-dihydro-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 214); (*R/S*)-9-Fluoro-1,2-dihydro-5-(4-methoxyphenyl)-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound 215); (*R/S*)-8-Fluoro-1,2-dihydro-5-methoxyl-2,2,4-trimethyl-*5H*-chromeno[3,4-*f*]quinoline (Compound

216); (*R/S*)-5-(4-Chlorophenyl)-8-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 217); and (*R/S*)-9-Chloro-5-(4-chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 218); 9-Chloro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 320); (*R/S*)-9-Fluoro-1,2-dihydro-5-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 322); (*R/S*)-9-Fluoro-1,2-dihydro-2,2,4-trimethyl-5-thiopropoxy-5*H*-chromeno[3,4-*f*]quinoline (Compound 323); (*R/S*)-9-Fluoro-1,2-dihydro-2,2,4-trimethyl-5-propoxy-5*H*-chromeno[3,4-*f*]quinoline (Compound 324); (*R/S*)-1,2-Dihydro-9-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 329); (*R/S*)-1,2-Dihydro-2,2,4,9-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 330); (*R/S*)-7-Chloro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 331); (*R/S*)-5-(4-Bromo-3-pyridyl)-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylidene-5*H*-chromeno[3,4-*f*]quinoline (Compound 347); (*R/S*)-5-(3,5-Difluorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 348); (*R/S*)-5-(3-Bromo-5-fluorophenyl)-1,2,3,4-tetrahydro-2,2-dimethyl-4-methylidene-5*H*-chromeno[3,4-*f*]quinoline (Compound 352); (*Z*)-1,2,-Dihydro-5-(2,4,6-trimethylbenzylidene)-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*quinoline (Compound 364); (*Z*)-5-Benzylidene-9-fluoro-1,2-dihydro-2,2,4,11-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 377); (*R/S*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]-4-quinolinone (Compound 378); (*R/S*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,3,3-tetramethyl-5*H*-chromeno[3,4-*f*]-4-quinolinone (Compound 379); (*R/S*)-5-(4-Chlorophenyl)-1,2-dihydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]-4-quinoline (Compound 380); (+)-(R*-4l,5l)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound 381); (-)-(R*-4l,5l)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound 382); (*R/S*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound 383); (*R/S*)-3-(3-Fluorobenzyl)-5-(3-fluorobenzylidene)-1,2,3,4-tetrahydro-3-hydroxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 384); (*R/S*)-3,5-Dibutyl-1,2,3,4-tetrahydro-3-hydroxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 385); (*R/S*)-5-Butyl-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound 386); (R/S-4l,5l)-1,2,3,4-Tetrahydro-2,2,4-trimethyl-5-phenyl-5*H*-

chromeno[3,4-*f*]-3-quinolinone (Compound 387); (*R/S-4l,5u*)-1,2,3,4-Tetrahydro-2,2,4-trimethyl-5-phenyl-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound 388); (*R/S-4l,6u*)-1,2,3,4-Tetrahydro-2,2,4-trimethyl-6-phenyl-5*H*-isochromeno[3,4-*f*]-3-quinolinone (Compound 390); (*R/S-4l,6l*)-1,2,3,4-Tetrahydro-2,2,4-trimethyl-6-phenyl-5H-isochromeno[3,4-*f*]-3-quinolinone (Compound 391); (*R/S-3l,4u,5u*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-3-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 397); (*R/S-3l,4u,5l*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-3-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 398); (*R/S-3l,4u,5l*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-3-propyloxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 399); (*R/S-3l,4u,5u*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-3-propyloxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 400); and (*R/S-4l,5l*)-3-Benzenzylidene-5-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 401).

10. A PR agonist compound according to claim 5 selected from the group consisting of (*Z*)-5-Butylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 219); (*Z*)-5-Benzylidene-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 220); (*Z*)-5-(4-Fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 221); (*Z*)-5-(4-Bromobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 222); (*Z*)-5-(3-Bromobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 223); (*Z*)-5-(3-Chlorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 224); (*Z*)-5-(3-Fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 225); (*Z*)-5-(2-Chlorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 226); (*Z*)-5-(2-Bromobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 227); (*Z*)-5-(2-Fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 228); (*Z*)-5-(2,3-Difluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 229); (*Z*)-5-(2,5-Difluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 230); (*Z*)-9-Fluoro-5-(3-fluorobenzylidene)-1,2-dihydro-2,2,4-

trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 231); (*Z*)-9-Fluoro-5-(3-methoxybenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 232); (*Z*)-8-Fluoro-5-(3-fluororbenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 233); (*R/S-4l*, *5u*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound 234); (*R/S-4l*, *5l*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound 235); and (*R/S*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4,4-tetramethyl-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound 236); 5-(3-Fluorobenzyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 318); (*R/S*)-9-Chloro-1,2-dihydro-2,2,4-trimethyl-5-propyloxy-5*H*-chromeno[3,4-*f*]quinoline (Compound 321); (*R/S*)-5-Butyl-9-chloro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 325); (*R/S*)-5-Butyl-1,2-dihydro-9-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 326); (*R/S*)-9-Fluoro-1,2-dihydro-2,2,4,5-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 327); (*R/S*)-9-Chloro-1,2-dihydro-2,2,4,5-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 332); (*R/S*)-5-(4-Bromophenyl)-9-chloro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 333); (*R/S*)-9-Chloro-5-(3-chlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 334); (*R/S*)-9-Chloro-1,2-dihydro-2,2,4-trimethyl-5-(3-methylphenyl)-5*H*-chromeno[3,4-*f*]quinoline (Compound 335); (*R/S*)-9-Chloro-5-(4-chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 336); (*R/S*)-9-Chloro-1,2-dihydro-5-[3-(trifluoromethyl)phenyl]-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 337); (*R/S*)-9-Chloro-5-(3,5-dichlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 338); (*R/S*)-9-Chloro-1,2-dihydro-5-(4-methoxyphenyl)-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 339); (*R/S*)-9-Chloro-5-(3-fluoro-4-methoxyphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 340); (*R/S*)-9-Chloro-5-(4-fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline(Compound 341); (*R/S*)-9-Chloro-5-(3-chloro-4-methoxy-5-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 342); (*R/S*)-9-Chloro-5-(4-fluoro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 343); (*R/S*)-9-Chloro-5-(3-fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-

chromeno[3,4-*f*]quinoline (Compound 344); (*R/S*)-1,2-Dihydro-2,2,4-trimethyl-5-[(3,4-methylenedioxy)phenyl]-5*H*-chromeno[3,4]-*f*quinoline (Compound 345); (*R/S*)-5-(4-Chloro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4]-*f*quinoline (Compound 346); (*R/S*)-5-(3,5-Dichlorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 349); (*R/S*)-5-(3-Bromo-5-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 350); (*R/S*)-5-(3-Bromo-5-fluorophenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 351); (*R/S*)-5-[4-Fluoro-3-(trifluoromethyl)phenyl]-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 353); (*R/S*)-9-Fluoro-1,2-dihydro-2,2,4-trimethyl-5-(3-methylphenyl)-5*H*-chromeno[3,4-*f*]quinoline (Compound 354); (*R/S*)-1,2-Dihydro-9-methoxy-2,2,4-trimethyl-5-(3-methylphenyl)-5*H*-chromeno[3,4-*f*]quinoline (Compound 355); (*R/S*)-9-Fluoro-5-(3-fluoro-4-methoxyphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 356); (*R/S*)-9-Fluoro-1,2-dihydro-2,2,4-trimethyl-5-[3-(trifluoromethyl)phenyl]-5*H*-chromeno[3,4-*f*]quinoline (Compound 357); (*R/S*)-9-Fluoro-5-(4-fluoro-3-methylphenyl)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 358); (*Z*)-5-(2,4-Difluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 359); (*Z*)-5-(3,4-Difluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*quinoline (Compound 360); (*Z*)-5-(3-Fluorobenzylidene)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 361); (*Z*)-5-(2,6-Difluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 362); (*Z*)-1,2,-Dihydro-5-(2-methylbenzylidene)-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 363); (*Z*)-9-Chloro-5-(2,5-difluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 365); (*Z*)-5-Benzylidene-9-chloro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 366); (*Z*)-9-Chloro-1,2-dihydro-2,2,4-trimethyl-5-(2-methylbenzylidene)-5*H*-chromeno[3,4-*f*]quinoline (Compound 367); (*Z*)-5-Benzylidene-9-chloro-1,2-dihydro-2,2-dimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 368); (*Z*)-9-Chloro-5-(2-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 369); (*Z*)-9-Chloro-5-(3-fluorobenzylidene)-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 370); (*E/Z*)-5-Benzylidene-9-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-

f]quinoline (Compound 371); (*Z*)-5-Benzylidene-8-fluoro-1,2-dihydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 372); (*Z*)-5-Benzylidene-1,2-dihydro-9-methoxy-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 373); (*Z*)-9-Fluoro-1,2-dihydro-2,2,4-trimethyl-5-(2-methylbenzylidene)-5*H*-chromeno[3,4-*f*]quinoline (Compound 374); (*Z*)-8-Fluoro-1,2-dihydro-2,2,4-trimethyl-5-(2-methylbenzylidene)-5*H*-chromeno[3,4-*f*]quinoline (Compound 375); (*Z*)-1,2-Dihydro-9-methoxy-2,2,4-trimethyl-5-(2-methylbenzylidene)-5*H*-chromeno[3,4-*f*]quinoline (Compound 376); (*Z*)-(*R/S*)-5-(3-Fluorobenzylidene)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound 389); (*Z*)-(*R/S*)-5-(Benzylidene)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound 392); (*R/S-4l,5u*)-5-(3-Fluorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound 393); (*R/S-4l,5l*)-5-(3-Fluorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound 394); (*R/S-4l,5l*)-1,2,3,4-Tetrahydro-2,2,4-trimethyl-5-[3-(trifluoromethyl)phenyl]-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound 395); (*R/S-4l,5u*)-1,2,3,4-Tetrahydro-2,2,4-trimethyl-5-[3-(trifluoromethyl)phenyl]-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound 396); (*R/S-4l,5u*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound 402); (*R/S-4l,5l*)-5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-5*H*-chromeno[3,4-*f*]-3-quinolinone (Compound 403); and (*R/S*)-5-Butyl-1,2-dihydro-2,2,4,9-tetramethyl-5*H*-chromeno[3,4-*f*]quinoline (Compound 457).

11. An AR modulator compound according to claim 6 selected from the group consisting of 1,2-Dihydro-2,2,4-trimethyl-6-methoxymethyl-8-pyranono[5,6-*g*]quinoline (Compound 237); 1,2-Dihydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyranono[5,6-g]quinoline (Compound 238); 1,2-Dihydro-2,2,4-trimethyl-10-isocoumarino[4,3-*g*]quinoline (Compound 239); 1,2-Dihydro-2,2,4-trimethyl-10-isoquinolono[4,3-*g*]quinoline(Compound 240); 1,2-Dihydro-2,2,4,6-tetramethyl-8-pyridono[5,6-*g*]quinoline (Compound 241); 1,2-Dihydro-10-hydroxy-2,2,4-trimethyl-10*H*-isochromeno[4,3-*g*]quinoline (Compound 242); 1, 2-Dihydro-2,2,4,6-tetramethyl-8H-pyrano[3,2-*g*]quinoline (Compound 243); (*R/S*)-1,2,3,4-Tetrahydro-2,2,4-trimethyl-10-isoquinolono[4,3-*g*]quinoline (Compound 244); 1,2-Dihydro-2,2,4-

trimethyl-10-thioisoquinolono[4,3-*g*]quinoline (Compound 245); (+)-1,2,3,4-Tetrahydro-2,2,4-trimethyl-10-isoquinolono[4,3-*g*]quinoline (Compound 246); 1,2-Dihydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 247); (*R/S*)-1,2,3,4-Tetrahydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound 250); 1,2-Dihydro-2,2,4-trimethyl-6-trifluoromethyl-8-thiopyranono[5,6-g]quinoline (Compound 251); (*R/S*)-1,2,3,4-Tetrahydro-2,2,4-trimethyl-6-trifluoromethyl-8-thiopyranono[5,6-*g*]quinoline (Compound 252); 6-Chloro(difluoro)methyl-1,2-dihydro-2,2,4-trimethyl-8-pyranono[5,6-*g*]quinoline (Compound 253); 9-Acetyl-1,2-dihydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 254); 1,2-Dihydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 255); 1,2-Dihydro-2,2,4-trimethyl-6-(1,1,2,2,2-pentafluoroethyl)-8-pyranono[5,6-g]quinoline (Compound 256); (*R/S*)-6-Chloro(difluoro)methyl-1,2,3,4-tetrahydro-2,2,4-trimethyl-8-pyranono[5,6-g]quinoline (Compound 257); 7-Chloro-1,2-dihydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound 258); (*R/S*)-7-Chloro-1,2,3,4-tetrahydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound 259); 1,2,3,4-Tetrahydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 260); 1,2-Dihydro-2,2,4,9-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 261); 1,2-Dihydro-2,2,4-trimethyl-8-trifluoromethyl-6-pyridono[5,6-*g*]quinoline (Compound 262); 6-[Dichloro(ethoxy)methyl]-1,2-dihydro-2,2,4-trimethyl-8-pyranono[5,6-*g*]quinoline (Compound 263); 5-(3-Furyl)-1,2-dihydro-2,2,4-trimethyl-8-pyranono[5,6-*g*]quinoline (Compound 264); 1,2-Dihydro-1,2,2,4-tetramethyl-6-trifluoromethyl-8-pyranono[5,6-g]quinoline (Compound 265); 1,2-Dihydro-6-trifluoromethyl-2,2,4-trimethyl-9-thiopyran-8-ono[5,6-*g*] quinoline (Compound 266); 1,2-Dihydro-1,2,2,4,9-pentamethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 267); 7-Chloro-1,2-dihydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 268); and 6-Chloro(difluoro)methyl-1,2-dihydro-2,2,4-trimethyl-8-pyridono[5,6-*g*]quinoline (Compound 269); (*R/S*)-1,2,3,4-Tetrahydro-1,2,2,4-tetramethyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound 404); (*R/S*)-5-(3-Furyl)-1,2,3,4-tetrahydro-2,2,4-trimethyl-8-pyranono[5,6-*g*]quinoline (Compound 405); 5-(3-Furyl)-1,2-dihydro-1,2,2,4-tetramethyl-8-pyranono[5,6-*g*]quinoline (Compound 406); 5-(3-Furyl)-1,2-dihydro-1,2,2,4-tetramethyl-8-

thiopyranono[5,6-*g*]quinoline (Compound 407); 6-Chloro-5-(3-furyl)-1,2-dihydro-1,2,2,4-tetramethyl-8-pyranono[5,6-*g*]quinoline (Compound 408); 1,2,3,4-Tetrahydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 409); (*R/S*)-1,2,3,4-Tetrahydro-4-methyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound 410); 1,2-Dihydro-2,2-dimethyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound 411); 1,2,3,4-Tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound 412); 1,2,3,4-Tetrahydro-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound 413); (*R/S*)-4-Ethyl-1,2,3,4-tetrahydro-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound 414); (*R/S*)-1,2,3,4-Tetrahydro-1,4-dimethyl-8-pyranono[5,6-*g*]quinoline (Compound 415); (*R/S*)-4-Ethyl-1,2,3,4-tetrahydro-1-methyl-8-pyranono[5,6-*g*]quinoline (Compound 416); 2,2-Dimethyl-1,2,3,4-tetrahydro-6-trifloromethyl-8-pyridono[5,6-*f*]quinoline (Compound 417); (*R/S*)-1,2,3,4-tetrahydro-6-trifluoromethyl-2,2,4-trimethyl-8-pyridono[5,6-*f*]-3-quinolinone (Compound 418); 5-Trifluoromethyl-7-pyridono[5,6-*e*]indoline (Compound 419); 8-(4-Chlorobenzoyl)-5-trifluoromethyl-7-pyridono[5,6-*e*]indoline (Compound 420); 7-*tert*-Butyloxycarbamoyl-1,2-dihydro-2,2,8-trimethylquinoline (Compound 421); 1,2,3,4-Tetrahydro-6-trifluoromethyl-8-pyridono[5,6-*f*]quinoline (Compound 422); 1,2-Dihydro-6-trifluoromethyl-1,2,2,4-tetramethyl-8-pyridono[5,6-*f*]quinoline (Compound 423); 3,3-Dimethyl-5-trifluoromethyl-7-pyridono[5,6-*e*]indoline (Compound 424); (*R/S*)-1,2,3,4-Tetrahydro-4-methyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (Compound 425); (*R/S*)-1,2,3,4-Tetrahydro-4-methyl-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (Compound 426); 1,2,2,-Trimethyl-1,2,3,4-tetrahydro-6-trifluromethyl-8-pyranono[5,6-*g*]quinoline (Compound 427); (*R/S*)-1,2,3,4-Tetrahydro-4-propyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound 428); 1,2,3,4-Tetrahydro-2,2,4-trimethyl-6-trifluoromethyl-9-thiopyran-8-ono[5,6-*g*]quinoline (Compound 429); 1,2-Dihydro-1,2,2,4-tetramethyl-6-trifluoromethyl-9-thiopyran-8-ono[5,6-*g*]quinoline (Compound 430); 1,2,3,4-Tetrahydro-1,2,2-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 431); 1,2,3,4-Tetrahydro-1-methyl-4-propyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound 432); 1,2,3,4-Tetrahydro-10-hydroxymethyl-2,2,4-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 433); 1,2,3,4-Tetrahydro-1,2,2,4-tetramethyl-6-trifluoromethyl-9-thiopyran-8-ono[5,6-*g*]quinoline (Compound 434); 1,2,3,4-Tetrahydro-

2,2,9-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 435); (*R*/*S*)-1,2,3,4-Tetrahydro-3-methyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 436); 1,2,3,4-Tetrahydro-3,3-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 437); (*R*/*S*)1,2,3,4-Tetrahydro-2,2,3-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 438); (*R*/*S*-2*l*,4*u*)-1,2,3,4-Tetrahydro-2,4-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 439); (*R*/*S*-2*l*,4*u*)-4-Ethyl-1,2,3,4-tetrahydro-2-methyl-6-trifluoromethyl-8-pyranono[5,6-*g*]quinoline (Compound 440); (*R*/*S*-2*l*,3*u*)-1,2,3,4-Tetrahydro-2,3-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 441); (*R*/*S*-2*l*,3*l*)-1,2,3,4-Tetrahydro-2,3-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 442); (*R*/*S*)-1,2,3,4-Tetrahydro-2,3,3-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 443); (*R*/*S*)-1,2,3,4-Tetrahydro-2-methyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 444); (*R*/*S*)-4-Ethyl-1,2,3,4-tetrahydro-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 445); (*R*/*S*-2*l*, 3*u*)-1,2,3,4-Tetrahydro-2,3,9-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 446); (*R*/*S*)-1,2,3,4-Tetrahydro-4-propyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (Compound 447); (*R*/*S*)-3-Ethyl-1,2,3,4-tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 448); (*R*/*S*)-1,2,3,4-Tetrahydro-2,2-dimethyl-6-trifluoromethyl-3-propyl-8-pyridono[5,6-*g*]quinoline (Compound 449); and 1-Methyl-5-trifluoromethyl-7-pyridono[5,6-*f*]indoline (Compound 450).

12. A compound according to claim 2, wherein the compound comprises an estrogen receptor agonist or antagonist.

13. A compound according to claim 2, wherein the compound comprises a glucocorticoid receptor agonist or antagonist.

14. A compound according to claim 2, wherein the compound comprises a mineralocorticoid receptor agonist or antagonist.

15. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

16. A pharmaceutical composition according to claim 15, wherein the composition is formulated for oral, topical, intravenous, suppository or parental administration.

17. A pharmaceutical composition according to claim 15, wherein the compound is administered to a patient as a dosage unit at from about 1μg/kg of body weight to about 500 mg/kg of body weight.

18. A pharmaceutical composition according to claim 15, wherein the compound is administered to a patient as a dosage unit at from about 10μg/kg of body weight to about 250 mg/kg of body weight.

19. A pharmaceutical composition according to claim 15, wherein the compound is administered to a patient as a dosage unit at from about 20μg/kg of body weight to about 100 mg/kg of body weight.

20. A pharmaceutical composition according to claim 15, wherein the composition is effective in treating and/or modulating human fertility, female hormone replacement, dysfunctional uterine bleeding, endometriosis, leiomyomas, acne, male-pattern baldness, osteoporosis, prostatic hyperplasia, cancer of the breast, cancer of the ovaries, endometrial cancer, prostate cancer, carbohydrate, protein and lipid metabolism, electrolyte and water balance, and functioning of the cardiovascular, kidney, central nervous, immune and skeletal muscle systems.